April 2009
Volume 2, Issue 4

CLINICAL TRIAL MAGNIFIER

US FDA site inspection findings during the post ICH period, 1997-2008, fail to justify clinical research globalization concerns as recently put forth in the US and EU

In this *Magnifier* issue we report, East Europe, with 150 completed US FDA site inspections, has the best overall results, with 3.3% of its site inspections having three or more deficiencies, compared with 20.2% in Europe. A significant, relatively higher number of deficiencies are also reported for European sites, notably 43.6% for "Failure to follow investigational plan", compared with 33.9% for North America and 27.5% for rest-of-the-world.

It is therefore ironic that the European Medicines Agency (EMEA) recently posted a strategy paper expressing growing concern about how well clinical trials are conducted from an ethical and scientific standpoint in regions outside Europe and North America, namely Africa, Asia, Latin America and Russia.

Our findings strongly imply that equal or even stronger concerns should be directed towards Western European investigator sites.

Next Issue

May 2009, Volume 2, Issue 5

Investigator Initiated Clinical Trial Contract Issues

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Contents of this Issue

"Get your facts first, then you can distort them as you please." -- Mark Twain.

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Your Site MATTERS,

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Magnifier Conference

We have progressed with the inaugural *Magnifier* 2009 Conference, scheduled for November 13-15, 2009 in Hong Kong. The conference program is detailed on the following pages.

It will address important issues related to clinical trials; with a specific focus on clinical trial agreements, budgets, regulations and operations. The conference will be of particular interest to either clinical research novices or veterans working with study sponsors, research sites or CROs.

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- Middle East: Israel
- Africa: South Africa, Tanzania
- Asia: China, India, Hong Kong, Malaysia, Singapore, South Korea, Taiwan, Thailand
- Oceania: Australian

We will continue to update this website over the course of the next six months leading up to the conference.

www.CTMConference.com

Registration will open by the end of May.

Study Site SOPs

In this *Magnifier* issue we have published two generic study site standard operating procedures – one for an audit and one for an inspection.

Those SOPs are short and comprehensive, and addresses the main matters related to such quality assurance on-site visits.

We plan to continue to publish our generic site SOPs that we have developed over the past decade. They are in total 24 and we will include two SOPs per Magnifier issue.

Comments on the SOPs are more than welcome. By time we plan to establish a standardizing committee based on those SOPs.

After revisions and complementation the full set of SOPs will be made available free-of-charge for the Magnifier's subscribers.

Hong Kong, April 2009

Magnifier Editorial Board

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INDIA represents an enormous opportunity in conduct of clinical trials.

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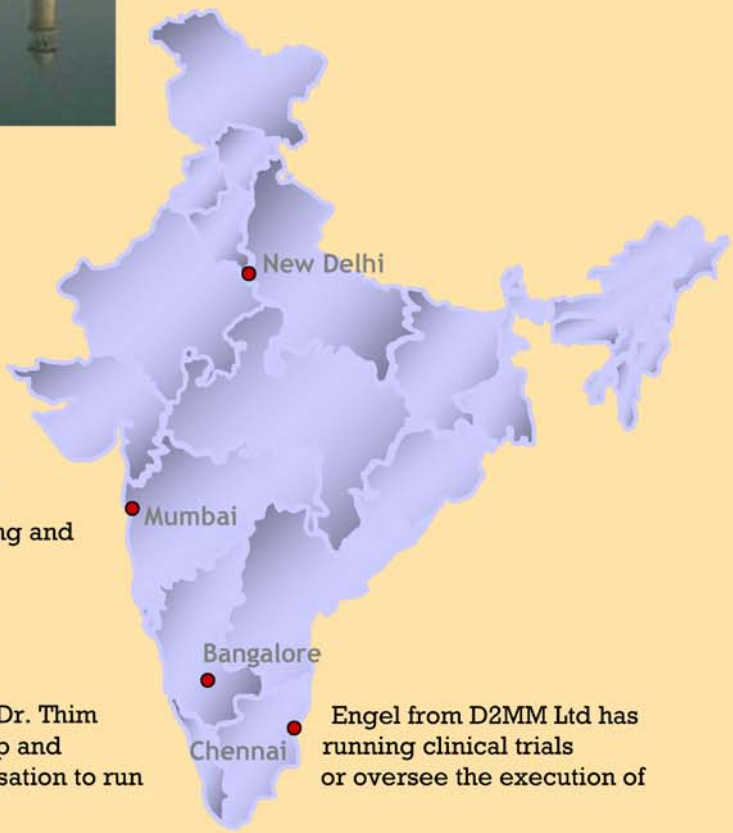
- Lack of Good Clinical Practice (GCP)-certified sites and investigators
- Inexperienced sponsor staff
- Need for frequent site monitoring and tight quality control
- Rapidly rising costs
- Availability of drugs after trial



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Kuala Lumpur Int'l Airport	4	Qatar Airways
Munich Airport	5	Emirates
Kansai Airport	6	Qantas
Copenhagen Airport	7	Etihad Airways
Zurich Airport	8	Air New Zealand
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S Pellegrino Worlds 100 Best Restaurants 2009	
Name of Restaurant	All Asian Locations
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RyuGin	Japan
Quintessence	Japan
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Wasabi	Indonesia
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Les Amis	Singapore
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Weather	Mean Temp. (C)		Mean Total	Mean #	Mean Temp. (F)	
Month	Daily Min.	Daily Max.	Rainfall (mm)	Rain Days	Daily Min.	Daily Max.
Jan	14.1	18.6	24.9	5.6	57.4	65.5
Feb	14.4	18.6	52.3	9.5	57.9	65.5
Mar	16.9	21.5	71.4	10.5	62.4	70.7
Apr	20.6	25.1	188.5	11.7	69.1	77.2
May	23.9	28.4	329.5	15.5	75.0	83.1
Jun	26.1	30.4	388.1	18.8	79.0	86.7
Jul	26.7	31.3	374.4	17.8	80.1	88.3
Aug	26.4	31.1	444.6	17.4	79.5	88.0
Sep	25.6	30.2	287.5	14.8	78.1	86.4
Oct	23.4	27.7	151.9	8.1	74.1	81.9
Nov	**19.4**	**24.0**	**35.1**	**5.7**	**66.9**	**75.2**
Dec	15.7	20.3	34.5	4.3	60.3	68.5

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Clinical Trial Magnifier *2009 Conference* – Hong Kong

Globalization and Standardization

Agreements - Budgets – Regulations - Operations

- ✓ The *Magnifier Conference* is focused on clinical trial agreements, budgets, regulations and operations.
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Conference Venue

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Clinical Trial Magnifier Conference 2009 Hong Kong

13-15 November

Globalization and Standardization

Agreements - Budgets - Regulations - Operation

Friday - November 13, 2009

12:00 - 20:00	**Registration**
13:00 - 13:15	**Chairman's Welcome and Housekeeping Remarks**
13:15 - 15:00	**MAGNIFIER's Workshops**
13:15 - 15:00	**Legal Requirements, Research Ethics and Informed Consent – The Basics**
13:15 - 13:35	Evolution of Human Research Ethics
13:35 - 13:55	IRB Accreditation?
13:55 - 14:15	Vulnerable Clinical Trial Subjects
14:15 - 14:35	Elements of Informed Consent Forms
14:35 - 14:55	Efficient Adverse Event Reporting
13:15 - 15:00	**Clinical Trial Players and Responsibilities – The Basics**
13:15 - 13:35	Clinical Trial Players and Responsibilities
13:35 - 13:55	Communicating with Regulatory Authority
13:55 - 14:15	The Perfect Sponsor
14:15 - 14:35	The Wonderful Investigator
14:35 - 14:55	The Devoted Study Coordinator
13:15 - 15:00	**Study Design – Novel Directions**
13:15 - 13:35	Pre-clinical Studies in Animal Patients
13:35 - 13:55	Naturalistic Clinical Trials
13:55 - 14:15	Paediatric Trials in Resource Limited Settings
14:15 - 14:35	Disease-modifying trials in Alzheimer's disease: challenges and emerging solutions
14:35 - 14:55	Novel therapeutics in Breast Cancer; do we still need chemotherapy?
15:00 - 15:20	**Coffee Break - Networking**
15:20 - 15:55	**Satellite Symposia**
15:20 - 15:55	Satellite Symposium I - The Importance of Clinical Pharmacology in Clinical Trials
15:20 - 15:55	Satellite Symposium II - The Impact of the EU Clinical Trial Directive 2001/02/EC
15:20 - 15:55	Satellite Symposium III - Developing Botanic Oncology Therapeutics under FDA Regulatory Framework
16:00 - 18:00	**MAGNIFIER's Workshops**
16:00 - 18:00	**Study Site Management – Established and Emerging Trial Networks**
16:00 - 16:20	Clinical Research Collaboration Network (CRCN) in Thailand
16:20 - 16:40	Joint Clinical Trial Management based on a US-European Consortium Model: Is this possible in Asia?
16:40 - 17:00	Korea National Enterprise for Clinical Trials (KoNECT)
17:00 - 17:20	Clinical Research in the UK: the Comprehensive Research Networks
17:20 - 17:40	Clinical Research Centre (CRC) in Malaysia
17:40 - 18:00	Optimizing Partnerships between Public and Private Organizations in Driving Clinical Research
16:00 - 18:00	**Clinical Trial Agreements and Budgets – The Basics**
16:00 - 16:20	Introduction to Clinical Trial Agreements
16:20 - 16:40	Concepts of Indemnification and Insurance
16:40 - 17:00	Principles of Investigator Initiated Trial Agreements
17:00 - 17:20	Introduction to Clinical Trial Budgets
17:20 - 17:40	Sensible Clinical Trial Payment Terms
17:40 - 18:00	Institutional Indirect and Administrative Fee
16:00 - 18:00	**Project Management and Monitoring – The Basics**
16:00 - 16:20	Essence of Project Management Skills
16:20 - 16:40	Selecting Responsible Monitors
16:40 - 17:00	Key Monitoring Roles and Responsibilities
17:00 - 17:20	Proficiency in Writing Monitor Reports and Follow-up Letters
17:20 - 17:40	Poor Site Interaction by Sponsor/CRO
17:40 - 18:00	Possible Clinical Research Professionals Career Pathways
18:00 - 20:30	**Cultural Reception - Networking**

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Clinical Trial Magnifier Conference 2009 Hong Kong

13-15 November

Saturday - November 14, 2009

08:00 - 08:45	**Registration**
08:45 - 09:00	**Opening Address**
09:00 - 11:00	**Regulations - Hot Topics**
09:00 - 10:00	PLENARY LECTURE: Current Trends in Regulation
10:00 - 10:30	Clinical Trial Register in Emerging Regions
10:30 - 11:00	Risk Management of First-into-man Trials
11:00 - 11:30	**Coffee Break - Networking**
11:30 - 13:00	**Research Ethics – Principal Population**
11:30 - 12:00	Ethical Problems with Illiteracy and no Access to Public Health Care
12:00 - 12:30	Ethical Problems with Clinical Trials in Russia
12:30 - 13:00	Educating Communities about Participating in Clinical Trials
13:00 - 14:00	**Lunch - Networking**
14:00 - 16:00	**Operation - Globalization**
14:00 - 15:00	PLENARY LECTURE: The Role of Asia in Global Drug Development
15:00 - 15:30	Why Clinical Trials in Eastern Europe?
15:30 - 16:00	How Does a Bio-Pharma go Global?
16:00 - 16:30	**Coffee Break - Networking**
16:30 - 18:00	**Magnifier Subscriber Surveys - Census Polling**
16:30 - 16:40	Clinical Research Guidelines
16:40 - 16:50	Clinical Trial Participation Incentives
16:50 - 17:00	Institutional Indirect Fee and Administrative Fee
17:00 - 17:10	Phase I Guideline
17:10 - 17:20	Investigator Initiated Trials
17:20 - 17:30	Clinical Trial Register
17:30 - 17:40	GCP/IRB Accreditation
17:40 - 17:50	Standardization
17:50 - 18:00	Summary
16:00 - 17:30	**MAGNIFIER's GCP & Research Administration Professional Exam (GRAPE)**
19:30	**Participants' Dinner –reserved tables/set menu/popular restaurants (no host)**
19:30	**Speakers' Dinner – by invitation**

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- ✓ 41 MD ± PhD
- ✓ 16 PhD, or similar
- ✓ 8 Master, MBA, or other
- ✓ In total 65 Faculty

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- ✓ North America: US, Canada
- ✓ Latin America: Brazil, Mexico
- ✓ Europe: Germany, The Netherlands, Sweden, Switzerland, United Kingdom
- ✓ East Europe: Bulgaria , Russia, Turkey, Ukraine
- ✓ Middle East: Israel
- ✓ Africa: South Africa, Tanzania
- ✓ Asia: China, India, Hong Kong, Malaysia, Singapore, South Korea, Taiwan, Thailand
- ✓ Oceania: Australian

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Clinical Trial Magnifier Conference 2009 Hong Kong

13-15 November

Sunday - November 15, 2009

08:00 - 09:00	**Registration**
09:00 - 11:00	**Budgets**
09:00 - 10:00	PLENARY LECTURE: Escalating Costs of Clinical Trials
10:00 - 10:30	Clinical Trial Budget Development
10:30 - 11:00	Negotiating Clinical Trial Budgets
11:00 - 11:30	**Coffee Break**
11:30 - 13:00	**Agreements**
11:30 - 12:00	Regional Discrepancies of Clinical Trial Agreements
12:00 - 12:30	Development of Clinical Trial Agreements
12:30 - 13:00	Negotiating Clinical Trial Agreements
13:00 - 14:00	**Lunch**
14:00 - 16:00	**Operation – Efficiency**
14:00 - 15:00	PLENARY LECTURE: Managing Global Studies
15:00 - 15:30	Clinical Research Centre Infrastructure Development
15:30 - 16:00	Getting Program, Study and Site Feasibility Right
16:00 - 16:30	**Coffee Break**
16:30 - 18:00	**Operation - Trial Performance and Incentives**
16:30 - 17:00	Trial Participation Incentives in Old and New EU Member States
17:00 - 17:30	Trial Performance in Europe, US and Australasia
17:30 - 18:00	US FDA Inspections in Established versus Emerging Regions
18:00 - 18:15	**Conference Summary and Closing**
18:15	**Announcement of Next Magnifier Conference**
16:00 - 17:30	**MAGNIFIER's GCP & Research Administration Professional Exam (GRAPE)**

Magnifier Conference website

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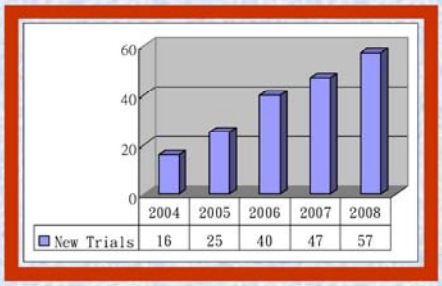

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US FDA Site Inspection Findings, 1997-2008, Fail to Justify Globalization Concerns

By Johan PE Karlberg, MD, PhD, BSc

Clinical Trials Centre, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, PR China

Summary

All US FDA site inspection findings were downloaded on March 12, 2009.

Between 1997 and 2008 there were 3,818 "valid" US FDA site inspections; 3,304 (86.5%) of them Data Audit inspections and 514 (13.5%) For Cause inspections.

The most common deficiencies identified are "Failure to follow investigational plan" (34.2%), "Inadequate and inaccurate records" (25.1%), "Inadequate drug accountability" (9.6%), "Inadequate informed consent form" (8.9%) and "Failure to report adverse drug reactions" (8.5%).

A statistical significantly higher number of deficiencies are reported for Western Europe than other regions.

Rest-of-the-world has in general somewhat better inspection results than North America, and North America has somewhat better results than Europe.

East Europe, with 150 completed US FDA inspections, has the best overall results.

Abstract

Since 1977 the US Food and Drug Administration (FDA) has conducted clinical site inspections under what is known as the Bioresearch Monitoring Program. Today it annually conducts several hundred inspections of clinical investigators, sponsors and IRBs to check compliance with regulations and ensure data submitted to the FDA is substantiated by appropriate records. This study analyzed the US FDA site inspection findings by geographic region from 1997 to the end of 2008 (12 full years), specifically focusing on inspections after the launch of the ICH GCP guideline in 1996. All site inspection findings were downloaded on March 12, 2009. Over the period there were 3,818 "valid" inspections; 3,304 (86.5%) of them Data Audit inspections and 514 (13.5%) For Cause inspections. This study convincingly shows a significant geographic difference in the deficiency findings of Data Audit clinical trial site inspections. In line with previous studies, the most common deficiencies identified are "Failure to follow investigational plan" (34.2%), "Inadequate and inaccurate records" (25.1%), "Inadequate drug accountability" (9.6%), "Inadequate informed consent form" (8.9%) and "Failure to report adverse drug reactions" (8.5%). Rest-of-the-world has somewhat better inspection results than North America, and North America has in general somewhat better results than Europe. We found that East Europe, with 150 completed US FDA inspections, has the best overall results. For instance, only 3.3% of East Europe site inspections reported three or more deficiencies, compared with 20.2% of sites in Europe. A significant relatively higher number of deficiencies are also reported for European sites, notably 43.6% for "Failure to follow investigational plan", compared with 33.9% for North America and 27.5% for RoW. It is therefore rather ironic that the European Medicines Agency (EMEA) recently posted a strategy paper expressing growing concern about how well clinical trials are conducted from an ethical and scientific standpoint in regions outside Europe and North America, namely Africa, Asia, Latin America and Russia. Our study strongly implies that similar or even stronger concerns should be directed towards Western European investigator sites.

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Introduction

EMEA, FDA to increase non-EU site inspections

The European Medicines Agency (EMEA) posted a strategy paper dated December 5, 2008 to the EMEA website announcing it is planning to join the US FDA in increasing the number of site inspections at clinical trial sites outside North America and Western Europe.[1] The EMEA states that approximately a quarter of the patients in pivotal clinical trials supporting European Economic Area marketing authorization applications between 2005-2008 came from Africa, Asia, Latin America, and Russia and other members of the Commonwealth of Independent States. Without any reference or objective source of information, it suggests: "There is growing concern both among regulators and in public debate about how well these trials are conducted from an ethical and scientific/organisational standpoint (including GCP compliance) and about the available framework for the supervision of these trials." The strategy paper also clarifies that forthcoming activities of the EMEA will also address the process of clinical development not only at the time of Marketing Authorization Application, but at earlier stages before and during the conduct of clinical trials.

Ethical and scientific implications of the globalization of clinical research

A recent paper making strong assertions that data for industry sponsored clinical trials conducted outside the established trial regions may not be ethical, scientifically sound or valid for extrapolation to established region populations was published in the *New England Journal of Medicine* on February 19, 2009. It was entitled "*Ethical and Scientific Implications of the Globalization of Clinical Research"* and the authors are affiliated to Duke University, North Carolina and The University of North Carolina, US.[2] It discusses recent trends and underlying reasons for globalization of clinical research, while highlighting important scientific and ethical concerns, and proposing steps for harmonizing international clinical research. Most of the source data supporting the assertive claims made by the authors are also missing.

How significant is globalization of clinical research?

As we have previously noted, the vast majority of clinical trial sites (87.1%) are still located in North America, the European community and other developed countries.[3] The concerns raised thus address the remaining 12.9% of trial sites. Of those, the vast majority (10.2%) are located in eight large populated countries - Argentina, Brazil, China, India, Mexico, Russia, South Africa and Ukraine - and 12,449 (75.3%) of them are large-scaled phase III trials, with almost all (except China) multi-national trials. This means that the studies are confirmatory in nature and not explorative early phase, high risk type. The vast majority are multi-national, following protocols accepted by the US FDA and/or the European Community, as well as the country specific regulatory authorities. Given this, it follows that only a very small proportion are in fact at risk of possible exposure to poor and unethical study design.

The quality of the data collected in developing countries can hardly be questioned either, since it is the responsibility of the sponsor to educate the investigators and ensure protocol is followed to the letter. To our knowledge, all industry sponsored trials have investigator meetings, site visits and audits, and continuous monitoring of source data and protocol compliance. Audit and monitoring is in line with standard operating procedures of international companies, as utilized in the established regions. The quality of data in emerging regions has in fact been reported to be as good as in established locations. The US FDA makes many overseas inspections and those performed worldwide show similar patterns of deficiencies almost regardless of region.[4]

Public disclosure of US FDA site inspection reports

The Investigational New Drug (IND) regulations in the US were established in 1963. Since 1977, the US Food and Drug Administration (FDA) has conducted clinical site inspections under what is known as the Bioresearch Monitoring Program. It annually conducts several hundred inspections of clinical investigators, sponsors and IRBs to monitor compliance with regulations and ensure data submitted to the FDA is substantiated by appropriate records. Most inspections are related to marketing application submissions and some to novel technology, vulnerable populations, "For Cause" inspections and complaints. More details about these FDA site inspections are below in "Materials and Methods". Results of the US FDA inspections - local or overseas - are publicly available on the FDA's home page; Center for Drug Evaluation and Research. It can thus be downloaded and analyzed.[5]

2004 Review of US FDA site inspections

We searched various data bases for reports on US FDA site inspections. There are a few presentations from meetings posted on the internet, but information is "thin on the ground" and not easy to understand or digest. However, we found one detailed report entitled "FDA Inspections Outside The USA: An Eastern European

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Perspective".[4] The report is based on FDA site inspection findings from January 1, 1994 to the end of 2003. In total, data from 3,178 inspections were reviewed; 2,765 from the US and 413 from non-US sites. The authors concluded that "despite rumours and existing prejudice, the Central and Eastern European region remains a solid and reliable arena for conducting clinical trials, in addition to the well-established clinical research sites in Canada and Western Europe. Clinical trials in these regions have been conducted since the early 1990s and have led to a generation of experienced professional clinical investigators, important to efficient and high-quality study conduct." To our knowledge, this is the only recent report based on US FDA findings on the performance of clinical trial sites in established as well as emerging trial regions.

ICH GCP Guideline – the door opener

The launch of the ICH GCP Guideline in 1996 opened the door for the globalization process of industry sponsored clinical trials.[6] As we all know, Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials involving human subjects. Compliance with this standard provides assurance that the rights, safety and well-being of trial subjects are protected, and clinical trial data credible. Its impact has been significant. By adopting the principles of the ICH GCP guideline, pharmaceutical companies can now collect trial data worldwide, rather than only in established regions, for filing new drug applications in established regions.

Study objectives

This study analyzed the US FDA site inspection findings by geographic region between 1977 and the end of 2008, specifically focusing on inspections after the launching of the ICH GCP guideline in 1996. It might provide solid and useful information supporting or disqualifying recent claims of negative ethical and scientific implications of the globalization of clinical research.

Materials and Methods

US FDA site inspections

A US FDA inspection is a quality assurance process used to verify clinical data and regulatory compliance. The most common type of inspection, the so-called "Data Audit" site inspection, is classified by the FDA as "routine" and generally triggered by a New Drug Application (NDA) submission.[5] Commonly, clinical investigators who enroll the most patients in pivotal NDA trials are the most likely candidates for a routine inspection. "For Cause" inspections are much more infrequent and generally arise only when the FDA receives reports or becomes aware of doubtful performance by a clinical investigator: whether for conducting many trials; conducting trials outside of field of specialization; reporting significantly better efficacy, fewer adverse effects, or different laboratory results than other investigators studying the same drug; having too many patients with a specific disease state; or complaints from a patient or sponsor. A third, but very uncommon type of site inspection, is "Information Gathering".

Inspections include detailed reviews of numerous trial-related documents such as the protocol, Investigator's Brochure and Safety Reports, CVs, IRB correspondence, IRB-approved informed consent form, IRB-approved advertising, study-related correspondence, monitor sign-in log, laboratory certification documents, drug accountability records, and each subject's signed informed consent.

After the site inspection visit, the inspector files an Establishment Inspection Report (EIR) for submission to the FDA for evaluation. The FDA's response to the investigator includes one of three possible Inspection Classification Codes: (1) No Action Indicated (NAI), acknowledging the inspection has been completed and no significant deficiencies have been found; (2) Voluntary Action Indicated (VAI), listing deficiencies noted during the investigation, but indicating that no specific response is necessary; and (3) Official Action Indicated (OAI), acknowledging serious negative findings identified by the inspector. To this, an immediate response is required to explain how these discrepancies will be addressed. Failure to adequately respond can result in the investigator being disqualified from conducting other studies, rejection of the study data and perhaps the entire marketing application, and even potential criminal proceedings. Criminal prosecution is commonly related to submission of false information to the sponsor. A few inspections are not given a "valid" Classification Code, such as "Case closed", "Cancelled" or "Washout", indicating that an inspection was initiated but no meaningful information could be obtained, or "MTF" (Case closed with a Memo to File) and "Reference".

US FDA Deficiency Codes

The US FDA has 22 Deficiency Codes for site inspections findings:[5]

- No deficiencies noted
- Records availability
- Failure to obtain and/or document subject consent
- Inadequate informed consent form
- Inadequate drug accountability
- Failure to follow investigational plan
- Inadequate and inaccurate records
- Unapproved concomitant therapy

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- Inappropriate payment to volunteers
- Unapproved use of drug before IND submission
- Inappropriate delegation of authority
- Inappropriate use/commercialization of IND
- Failure to list additional investigators on 1572
- Subjects receiving simultaneous investigational drugs
- Failure to obtain or document IRB approval
- Failure to notify IRB of changes, failure to submit progress reports
- Failure to report adverse drug reactions
- Submission of false information
- Other
- Failure to supervise or personally conduct the clinical investigation
- Failure to protect the rights, safety, and welfare of subjects
- Failure to permit FDA access to records

Table 1. Number of US FDA site inspections by year for all Inspection Classification Codes* and all Inspection Type Codes** pooled together.

Year	No Action n	Voluntary Action n	Official Action n	Closed n	Cancelled n	Washout n	Reference n	Total n
Unknown	1	0	1	1	100	102	0	205
1977	11	27	3	0	0	0	0	41
1978	28	55	13	0	1	0	0	97
1979	78	91	12	0	2	4	0	187
1980	79	136	17	0	1	0	0	233
1981	39	182	13	0	0	3	0	237
1982	34	140	4	0	2	0	0	180
1983	35	162	10	0	0	0	0	207
1984	43	200	8	0	0	0	0	251
1985	39	197	4	0	0	0	0	240
1986	34	167	9	0	0	0	0	210
1987	41	201	8	0	0	0	0	250
1988	46	208	10	0	1	1	0	266
1989	30	186	3	0	6	0	0	225
1990	37	204	8	0	24	0	0	273
1991	37	191	2	0	53	1	0	284
1992	56	219	3	0	40	2	0	320
1993	48	146	12	0	37	0	0	243
1994	35	155	7	0	22	0	0	219
1995	105	224	7	0	26	1	0	363
1996	165	226	13	0	39	2	0	445
1997	141	180	17	0	5	0	0	343
1998	122	172	14	0	6	0	0	314
1999	161	186	10	0	2	6	0	365
2000	137	201	12	0	7	5	0	362
2001	96	184	9	2	4	6	0	301
2002	117	178	7	0	0	4	0	306
2003	116	211	6	2	0	2	2	339
2004	101	205	8	7	4	0	0	325
2005	155	169	13	0	0	0	0	337
2006	174	167	18	2	0	0	0	361
2007	179	114	17	2	0	0	0	312
2008	124	97	1	1	0	0	0	223
Total	*2,644*	*5,381*	*299*	*17*	*382*	*139*	*2*	*8,864*

* Inspection Classification Code:

NAI No Action Indicated. No objectionable conditions or practices were found during the inspection.
VAI Voluntary Action Indicated. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.
OAI Official Action Indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.
MTF Case closed with a Memo to File
CANC Cancelled. The inspection assignment was canceled before the inspection was started.
WASH Washout. An inspection was initiated but no meaningful information could be obtained.
REF Reference

** Inspection Type Codes

DA Data Audit: An inspection in which the focus is on verification of study data.
FC For Cause: An inspection in which the focus is on the conduct of the study by the Clinical Investigator.
IG Information Gathering

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Material

The US FDA site inspection web site was accessed on March 12, 2009 and the full data set was downloaded, coded and subsequently analysed using the SAS (Statistical Analysis System) software.[7] The data included the following variables: record ID; name of investigator with affiliated institution, address, city, state, country and zip code; data of onsite inspection; Inspection Type Code; Inspection Classification Code; and Inspection Deficiency Code(s).

Results

Inspections distributed over classifications and types

From all the US FDA site inspection findings downloaded up to the end of 2008, there were 8,864 such inspections (Table 1); with 93.9% having a "valid" Inspection Classification Code, i.e. No Action Indicated (NAD), Volunteer Action Indicated (VAI) or Official Action Indicated (OAI). Of the remaining (6.1%), the majority (4.3% of all inspections) were classified as Washout (Wash), i.e. the inspection was initiated but no meaningful information could be obtained. The year by year distribution of the different classification types are shown in Figure 1. Note a rapid increase from 1977 to 1981, and another increase from 1995.

The numbers given in Table 1 and Figure 1 include information on the three US FDA Inspection Type Codes: namely DA – Data Audit – focusing on verification of study data; FC – For Cause – focusing on conduct of the study by the Clinical Investigator; and IG – Information Gathering – which was only coded for one single inspection, so the inspection was deleted from the analysis.

Based on the three "valid" Inspection Classification Codes, there were 7,386 (88.7%) Data Audit site inspections and 937 (11.3%) For Cause site inspections. Of the For Cause inspections, 923 (98.5%) were on US trial sites, seven in Canada, three in South Africa, one each in Malawi, Guatemala, and Costa Rica, and one in a non-defined country.

Table 2 and Figure 2 indicate the number of US FDA inspections by year and by the two common types of site inspections – namely Data Audit or For Cause – and by the three common Inspection Classification Codes: No Action, Voluntary Action and Official Action. Note the annual total number of inspections increased from 1995 from 200+ to 300+. The number of For Cause inspections doubled from 2000.

Post ICH GCP – 1997 to 2008

Between 1997 and 2008 there were 3,818 "valid" US FDA site inspections: 3,304 (86.5%) Data Audit inspections and 514 (13.5%) For Cause (Table 2). Distribution of inspection classification types clearly differs for the two types of inspections; 45.9% of the Data Audit inspections were classified as No Action compared to 20.4% for For Cause. The "risk" of obtaining an Official Action Classification Code is 6.9 times higher for For Cause inspections than Data Audit; 13.2% versus 1.9%. Note the relative distribution of Inspection Classification Codes varies over the years; for instance with relatively more Official Action classifications in 1997 and 1998 than later years (Figure 3).

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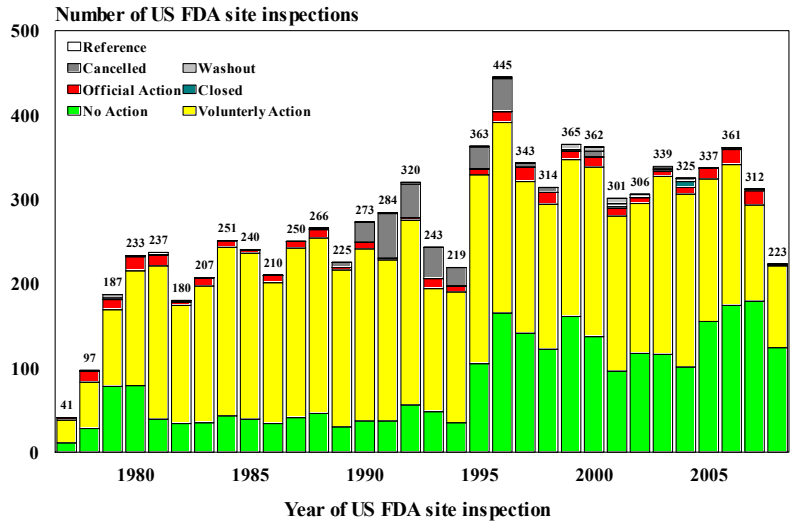

Figure 1. Total number of US FDA site inspections by year for all Inspection Classification Codes and all Inspection Type Codes. Values from Table 1.

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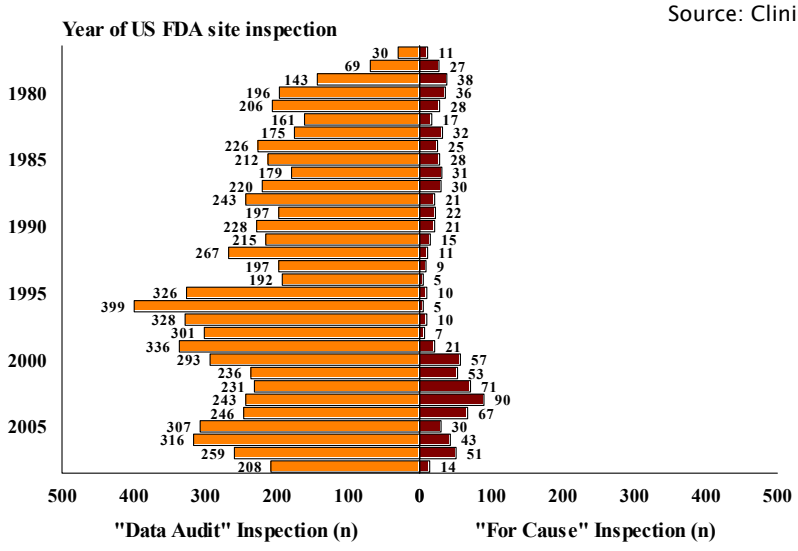

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Figure 2. Number of US FDA site inspections by year and by the two common types of inspections – Data Audit or For Cause – based on the three common Inspection Classification Codes, e.g. No Action, Voluntary Action and Official Action. Values from Table 2.

Table 2. Number of US FDA inspections by year and by the two common types of site inspections – e.g. Data Audit or For Cause – and by the three common or "valid" Inspection Classifications Codes – e.g. No Action, Voluntary Action and Official Action. For Cause inspections are predominantly made on US sites; 923 or 98.5%.

	Data Audit				For Cause				
Year	No Action n	Voluntary Action n	Official Action n	Total n	No Action n	Voluntary Action n	Official Action n	Total n	Grand Total n
Unknown	1	0	0	1	0	0	1	1	2
1977	5	25	0	30	6	2	3	11	41
1978	17	51	1	69	11	4	12	27	96
1979	55	87	1	143	23	4	11	38	181
1980	61	127	8	196	18	9	9	36	232
1981	29	175	2	206	10	7	11	28	234
1982	30	131	0	161	4	9	4	17	178
1983	31	143	1	175	4	19	9	32	207
1984	39	186	1	226	4	14	7	25	251
1985	33	177	2	212	6	20	2	28	240
1986	29	148	2	179	5	19	7	31	210
1987	39	181	0	220	2	20	8	30	250
1988	45	195	3	243	1	13	7	21	264
1989	30	167	0	197	0	19	3	22	219
1990	37	191	0	228	0	13	8	21	249
1991	36	179	0	215	1	12	2	15	230
1992	55	210	2	267	1	9	1	11	278
1993	48	141	8	197	0	5	4	9	206
1994	35	152	5	192	0	3	2	5	197
1995	104	216	6	326	1	8	1	10	336
1996	165	223	11	399	0	3	2	5	404
1997	141	175	12	328	0	5	5	10	338
1998	120	171	10	301	2	1	4	7	308
1999	160	170	6	336	1	16	4	21	357
2000	125	166	2	293	12	35	10	57	350
2001	87	146	3	236	9	38	6	53	289
2002	101	129	1	231	16	49	6	71	302
2003	106	135	2	243	10	76	4	90	333
2004	90	155	1	246	11	49	7	67	313
2005	149	149	9	307	6	20	4	30	337
2006	165	141	10	316	9	26	8	43	359
2007	156	96	7	259	23	18	10	51	310
2008	118	89	1	208	6	8	0	14	222
Total	*2,442*	*4,827*	*117*	*7,386*	*202*	*553*	*182*	*937*	*8,323*
1997–2008, n	*1.528*	*1,722*	*64*	*3,304*	*105*	*341*	*68*	*514*	*3,818*
1997–2008, %	*45.9*	*52.1*	*1.9*	*100.0*	*20.4*	*66.3*	*13.2*	*100.0*	

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Geographic distribution of Data Audit US FDA inspections

The vast majority of the US FDA Data Audit site inspections (2,711, 82.1%) were conducted in North America, i.e. the US and Canada (Table 3). Figures 4-5 show the absolute number of these in North America, Europe and rest-of-the-world (including East Europe). The number of rest-of-the-world inspections increased from 20 in 1990-1996 to 73 and 233, respectively, in 1997-2002 and 2003-2008. The number of inspections has recently decreased in Europe, from 2003-2008 for the first time far fewer (128) than in the rest-of-the-world (233).

Table 4 and Figures 6-7 detail Data Audit inspections for all continents and countries from 1997-2008. Figure 6 indicates the 20 countries with the highest number of inspections, with both Russia and Poland among the top six most inspected countries. Table 4 and Figure 6 also provide the percentage with No Action classification, showing some variation between the top countries. For instance, France has 22.9% and UK 35.8%, compared with 56.3% for Russia and 47.4% for Poland. Figure 7 gives the figures based on geographic regions, with the highest Official Action classification for Europe (3.5%), compared with 1.6% for the rest-of-the-world.

Figure 8 shows Europe has fewer No Action classifications than both North America and RoW, although the difference is not statistically significant.

Deficiency Codes in the US for Data Audit and For Cause Inspections

Statistical distribution of Deficiency Codes following inspections between 1997 and 2008 in the United States with the three "valid" inspection classifications are in Table 5 and Figure 9 both for Data Audit and For Cause inspections. Most percentages are significantly different between the two types of inspections. For instance, the 95% confidence interval is 32.4-36.0% and 51.8-60.5% for "Failure to follow investigational plan" for Data Audit and For Cause site inspections, respectively.

Deficiency Codes by geographic area for Data Audit Inspections

Statistical distribution of Deficiency Codes following inspections between 1997 and 2008 for the three "valid" inspection classifications is provided by geographic region in Table 6 and Figures 10-11. The most common type of deficiencies are "Failure to follow investigational plan" (34.2%), "Inadequate and inaccurate records" (25.1%), "Inadequate drug accountability" (9.6%), "Inadequate informed consent form" (8.9%) and "Failure to report adverse drug reactions" (8.5%), (Figure 10).

The 95% confidence limit for those five most deficient types are in Figures 11a-e for North America, Europe and rest-of-the-world. Note, North America and rest-of-the-

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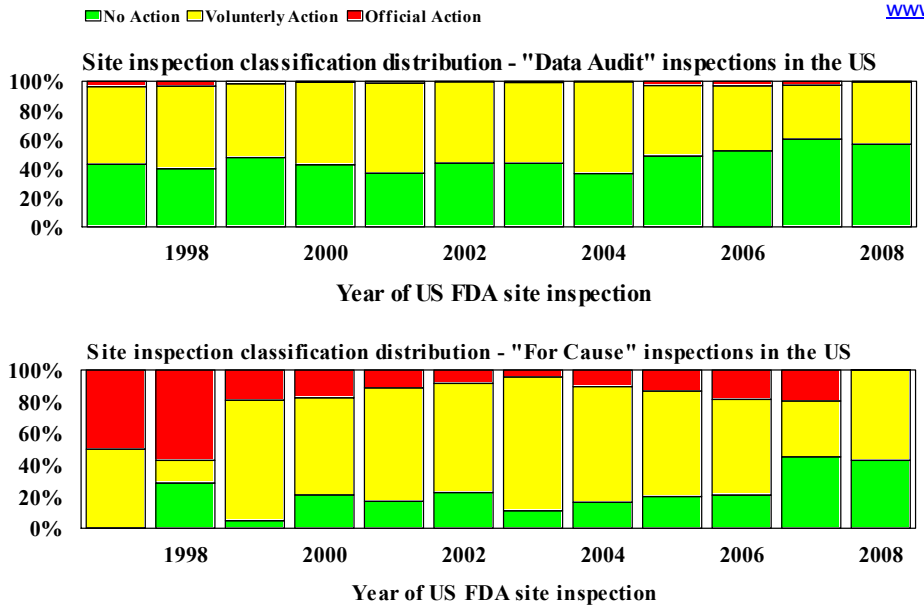

Figure 3. Number of US FDA site inspections between 1997 and 2008 and by the two common types of inspections - Data Audit or For Cause - and by the three common Inspection Classification Codes, e.g. No Action, Voluntary Action and Official Action. Values from Table 2.

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world have similar values, while Europe has higher values, especially for "Failure to follow investigational plan" and "Inadequate informed consent form". Rest-of-the-world has, in fact, a significantly lower proportion of "inadequate informed consent form" than both North America and Europe.

The proportionate number of identified deficiencies is not the same for different geographic regions. For instance, Europe averages 1.30 deficiencies per site inspection, compared with 1.02 for North America and 0.71 for East Europe (Table 6). This relationship is further elaborated in Figure 12, with 20.2% of the European sites having three or more deficiencies, versus 13.4 in North America and 6.5% in rest-of-the-world. The statistical distribution here is statistically significant between the three geographic regions. RoW has significantly fewer identified deficiencies per site than both North America and Europe. North America has significantly fewer than Europe. East Europe is the only rest-of-the world region with a relative large sample size – 150 site inspections. Of these, 53.3% of sites have no identified deficiency, 43.3% have one to two and 3.3% have over two. This East European distribution significantly differs from North America ($p<0.002$) and Europe (<0.0001).

Data Audit Inspection Classification for US States

Figure 13 gives the proportion – % and 95% confidence limit – of No Action classification for inspections between 1997 and 2008 in all US States having over 50 inspections. For instance California, Florida and New York State all have a significantly lower proportion of No Action classifications than Texas.

Table 3. Number of US FDA Data Audit inspections by year and by the geographic regions. For Cause inspections are not included here since they are predominantly made on US sites; n=923 or 98.5%.

Data Audit Year	North America n	Latin America n	Europe n	East Europe n	Middle East n	Africa n	Asia n	Oceania n	Total n
Unknown	1	0	0	0	0	0	0	0	1
1977	30	0	0	0	0	0	0	0	30
1978	69	0	0	0	0	0	0	0	69
1979	143	0	0	0	0	0	0	0	143
1980	190	5	0	0	0	0	0	1	196
1981	205	0	1	0	0	0	0	0	206
1982	161	0	0	0	0	0	0	0	161
1983	174	0	0	0	0	0	0	0	174
1984	224	0	1	0	0	0	1	0	226
1985	208	0	4	0	0	0	0	0	212
1986	178	1	0	0	0	0	0	0	179
1987	218	0	2	0	0	0	0	0	220
1988	238	0	1	0	0	0	1	0	240
1989	184	0	11	0	0	0	0	2	197
1990	220	0	5	0	0	0	1	0	226
1991	208	0	7	0	0	0	0	0	215
1992	253	0	11	0	3	0	0	0	264
1993	181	0	15	0	0	0	0	1	197
1994	171	0	17	2	0	2	0	0	192
1995	301	1	22	2	0	0	0	0	326
1996	372	4	18	1	1	0	0	3	398
1997	288	2	34	1	0	2	1	0	328
1998	255	1	32	8	0	3	2	0	301
1999	285	2	37	4	0	3	1	4	336
2000	250	1	30	5	1	6	0	0	293
2001	206	5	18	3	0	3	1	0	236
2002	209	7	8	2	0	2	3	0	231
2003	204	7	15	15	0	2	0	0	243
2004	179	13	30	18	0	2	3	1	246
2005	252	15	26	8	0	2	4	0	307
2006	242	9	22	28	0	2	11	2	316
2007	174	14	24	35	0	2	10	0	259
2008	167	5	11	23	0	2	0	0	208
Total	*6,640*	*92*	*402*	*155*	*5*	*33*	*39*	*14*	*7,375*
1997-2008, n	*2,711*	*81*	*287*	*150*	*1*	*31*	*36*	*7*	*3,304*
%	82.1	2.5	8.7	4.5	0.0	0.9	1.1	0.2	100.0

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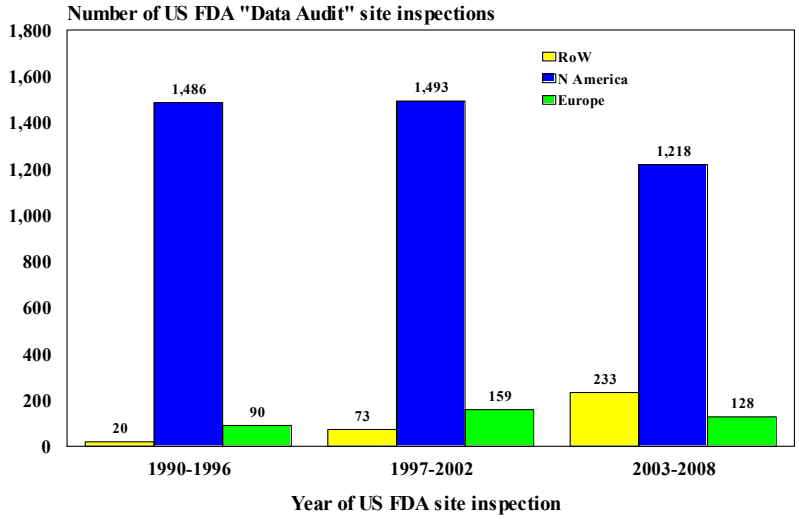

Figure 4. Number of US FDA Data Audit site inspections between 1991–1996, 1997–2002 and 2003–2008, respectively by geographic region. Values from Table 3.

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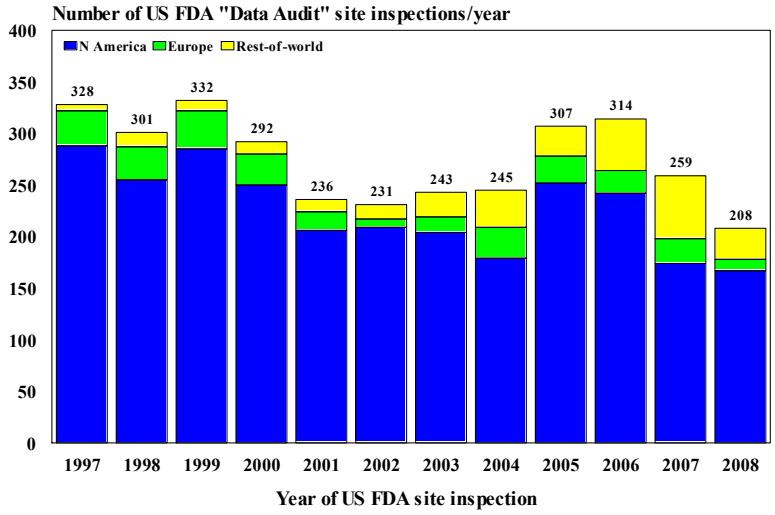

Figure 5. Number of US FDA Data Audit site inspections between 1997 and 2008 by geographic region. Values from Table 3.

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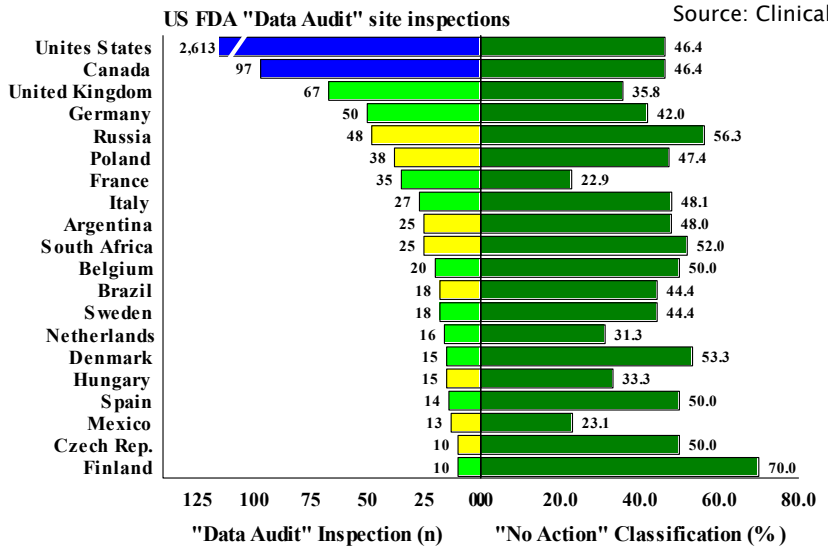

Figure 6. Number of US FDA Data Audit site inspections between 1997 and 2008 by country; the proportion of inspections classified as No Action is also provided. Values from Table 4.

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Table 4. Number of US FDA Data Audit site inspections between 1997 and 2008 by geographic region and by the three common Inspection Classification Codes, e.i. No Action, Voluntary Action and Official Action.

Continent Region	Country Region	No Action n	%	Voluntary Action n	%	Official Action n	%	Total n	%
North America	Unites States	1,212	46.4	1,352	51.8	49	1.9	2,614	100.0
North America	Canada	45	46.4	52	53.6	0	0.0	97	100.0
	Total	*1,257*	*46.4*	*1,405*	*51.8*	*49*	*1.8*	*2,711*	*100.0*
Latin America	Argentina	12	48.0	12	48.0	1	4.0	25	100.0
Latin America	Brazil	8	44.4	10	55.6	0	0.0	18	100.0
Latin America	Mexico	3	23.1	10	76.9	0	0.0	13	100.0
Latin America	Chile	4	50.0	4	50.0	0	0.0	8	100.0
Latin America	Costa Rica	2	33.3	4	66.7	0	0.0	6	100.0
Latin America	Peru	3	60.0	1	20.0	1	20.0	5	100.0
Latin America	Guatemala	1	50.0	1	50.0	0	0.0	2	100.0
Latin America	Panama	1	50.0	1	50.0	0	0.0	2	100.0
Latin America	Columbia	0	0.0	1	100.0	0	0.0	1	100.0
Latin America	Ecuador	1	100.0	0	0.0	0	0.0	1	100.0
	Total	*35*	*43.2*	*44*	*54.3*	*2*	*2.5*	*81*	*100.0*
Europe	United Kingdom	24	35.8	40	59.7	3	4.5	67	100.0
Europe	Germany	21	42.0	29	58.0	0	0.0	50	100.0
Europe	France	8	22.9	27	77.1	0	0.0	35	100.0
Europe	Italy	13	48.1	12	44.4	2	7.4	27	100.0
Europe	Belgium	10	50.0	8	40.0	2	10.0	20	100.0
Europe	Sweden	8	44.4	10	55.6	0	0.0	18	100.0
Europe	Netherlands	5	31.3	9	56.3	2	12.5	16	100.0
Europe	Denmark	8	53.3	7	46.7	0	0.0	15	100.0
Europe	Spain	7	50.0	6	42.9	1	7.1	14	100.0
Europe	Finland	7	70.0	3	30.0	0	0.0	10	100.0
Europe	Austria	2	40.0	3	60.0	0	0.0	5	100.0
Europe	Norway	2	40.0	3	60.0	0	0.0	5	100.0
Europe	Greece	0	0.0	2	100.0	0	0.0	2	100.0
Europe	Switzerland	1	50.0	1	50.0	0	0.0	2	100.0
Europe	Ireland	0	0.0	1	100.0	0	0.0	1	100.0
	Total	*116*	*40.4*	*161*	*56.1*	*10*	*3.5*	*287*	*100.0*
East Europe	Russia	27	56.3	20	41.7	1	2.1	48	100.0
East Europe	Poland	18	47.4	20	52.6	0	0.0	38	100.0
East Europe	Hungary	5	33.3	10	66.7	0	0.0	15	100.0
East Europe	Czech Rep.	5	50.0	5	50.0	0	0.0	10	100.0
East Europe	Turkey	1	16.7	4	66.7	1	16.7	6	100.0
East Europe	Bulgaria	4	80.0	1	20.0	0	0.0	5	100.0
East Europe	Estonia	2	40.0	3	60.0	0	0.0	5	100.0
East Europe	Latvia	1	20.0	4	80.0	0	0.0	5	100.0
East Europe	Ukraine	4	80.0	1	20.0	0	0.0	5	100.0
East Europe	Croatia	2	50.0	2	50.0	0	0.0	4	100.0
East Europe	Romania	3	75.0	1	25.0	0	0.0	4	100.0
East Europe	Lithuania	1	50.0	1	50.0	0	0.0	2	100.0
East Europe	Serbia	0	0.0	2	100.0	0	0.0	2	100.0
East Europe	Slovenia	1	100.0	0	0.0	0	0.0	1	100.0
	Total	*74*	*49.3*	*74*	*49.3*	*2*	*1.3*	*150*	*100.0*
Middle East	Israel	0	0.0	1	100.0	0	0.0	1	100.0
	Total	*0*	*0.0*	*1*	*100.0*	*0*	*0.0*	*1*	*100.0*
Africa	South Africa	13	52.0	11	44.0	1	4.0	25	100.0
Africa	Malawi	1	50.0	1	50.0	0	0.0	2	100.0
Africa	Egypt	1	100.0	0	0.0	0	0.0	1	100.0
Africa	Gabon	1	100.0	0	0.0	0	0.0	1	100.0
Africa	Kenya	1	100.0	0	0.0	0	0.0	1	100.0
Africa	Zambia	1	100.0	0	0.0	0	0.0	1	100.0
	Total	*18*	*58.1*	*12*	*38.7*	*1*	*3.2*	*31*	*100.0*
Asia	India	4	50.0	4	50.0	0	0.0	8	100.0
Asia	China	0	0.0	7	100.0	0	0.0	7	100.0
Asia	Hong Kong	1	20.0	4	80.0	0	0.0	5	100.0
Asia	Philippines	4	80.0	1	20.0	0	0.0	5	100.0
Asia	Thailand	2	50.0	2	50.0	0	0.0	4	100.0
Asia	Taiwan	2	66.7	1	33.3	0	0.0	3	100.0
Asia	South Korea	0	0.0	2	100.0	0	0.0	2	100.0
Asia	Malysia	1	100.0	0	0.0	0	0.0	1	100.0
Asia	Singapore	1	100.0	0	0.0	0	0.0	1	100.0
	Total	*15*	*41.7*	*21*	*58.3*	*0*	*0.0*	*36*	*100.0*
Oceania	Australia	1	25.0	3	75.0	0	0.0	4	100.0
Oceania	New Zealand	2	66.7	1	33.3	0	0.0	3	100.0
	Total	*3*	*42.9*	*4*	*57.1*	*0*	*0.0*	*7*	*100.0*

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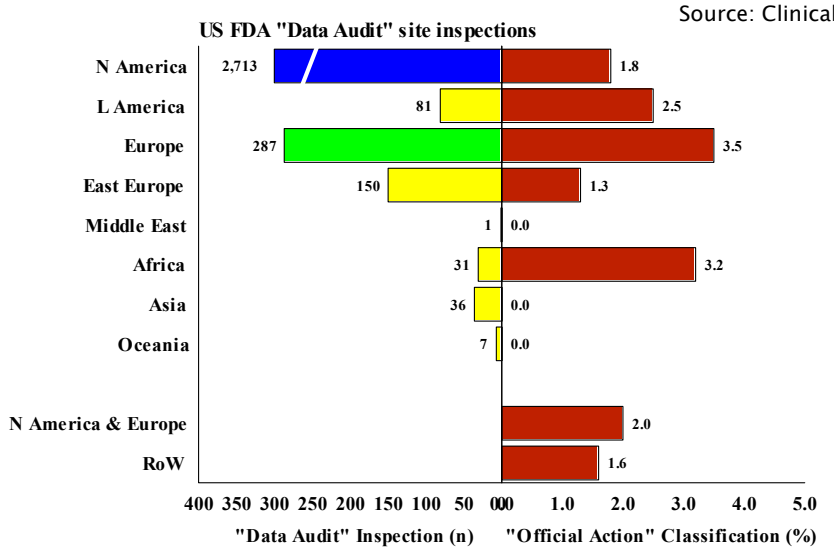

Figure 7. Number of US FDA Data Audit site inspections between 1997 and 2008 by geographic region; the proportion of inspections classified as Official Action is also provided. Values from Table 4.

Source: Clinical Trial Magnifier Vol. 2:4 Apr 2009
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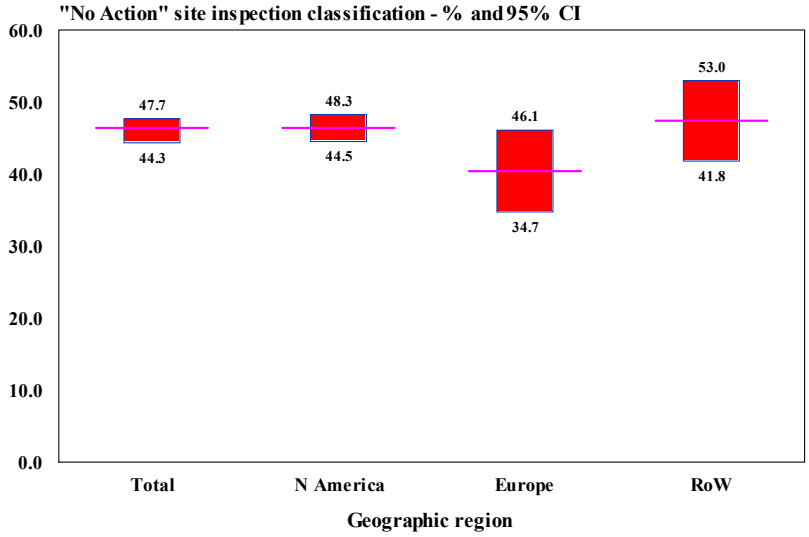

Figure 8. Proportion – % and 95% confidence limit – for the number of US FDA Data Audit site inspections classified as No Action between 1997 and 2008 by geographic region. Values from Table 4.

Source: Clinical Trial Magnifier Vol. 2:4 Apr 2009
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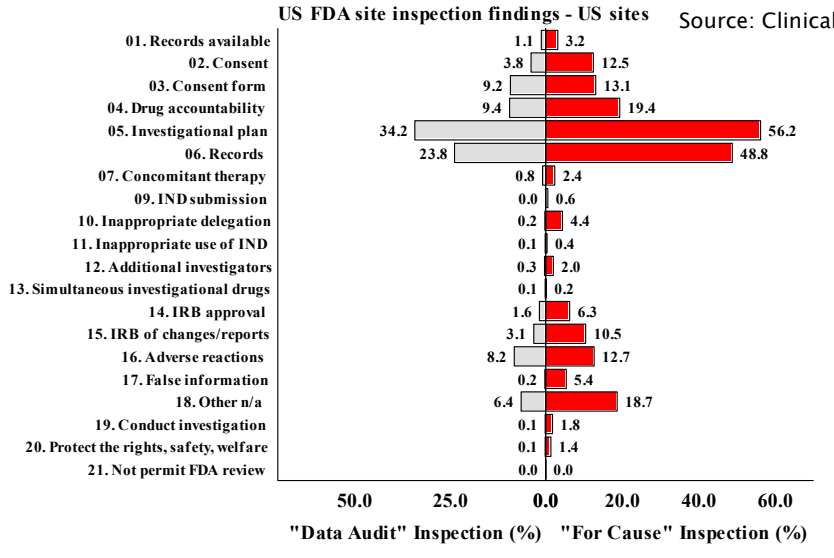

Figure 9. Proportion of deficiency type findings based on US FDA Data Audit and For Cause site inspections, respectively between 1997 and 2008 in the US only. Values from Table 5.

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Table 5. The statistical distribution of the Deficiency Codes following US FDA site inspections between 1997 and 2008 in the United States by the three common inspection classifications, i.e. No Action, Voluntary Action and Official Action. Values are provided for both for Data Audit Inspections and for For Cause Inspections.

Unites States only	No Action	Deficiency		Volun-tary Action	Deficiency		Official Action	Deficiency		Total	Deficiency	
Deficiency code	n	n	%	n	n	%	n	n	%	n	n	%
Data Audit Site Inspection												
01. Records availability	1,212	0	0.0	1,352	23	1.7	49	5	10.2	2,613	28	1.1
02. Failure to obtain and/or document subject consent	1,212	0	0.0	1,352	90	6.7	49	10	20.4	2,613	100	3.8
03. Inadequate informed consent form	1,212	0	0.0	1,352	226	16.7	49	14	28.6	2,613	240	9.2
04. Inadequate drug accountability	1,212	0	0.0	1,352	231	17.1	49	15	30.6	2,613	246	9.4
05. Failure to follow investigational plan	1,212	0	0.0	1,352	858	63.5	49	36	73.5	2,613	894	34.2
06. Inadequate and inaccurate records	1,212	0	0.0	1,352	585	43.3	49	38	77.6	2,613	623	23.8
07. Unapproved concomitant therapy	1,212	0	0.0	1,352	20	1.5	49	0	0.0	2,613	20	0.8
09. Unapproved use of drug before IND submission	1,212	0	0.0	1,352	0	0.0	49	1	2.0	2,613	1	0.0
10. Inappropriate delegation of authority	1,212	0	0.0	1,352	4	0.3	49	1	2.0	2,613	5	0.2
11. Inappropriate use/commercialization of IND	1,212	0	0.0	1,352	3	0.2	49	0	0.0	2,613	3	0.1
12. Failure to list additional investigators on	1,212	0	0.0	1,352	8	0.6	49	0	0.0	2,613	8	0.3
13. Subjects receiving simultaneous investigational drugs	1,212	0	0.0	1,352	2	0.1	49	0	0.0	2,613	2	0.1
14. Failure to obtain or document IRB approval	1,212	0	0.0	1,352	38	2.8	49	5	10.2	2,613	43	1.6
15. Failure to notify IRB of changes/progress reports	1,212	0	0.0	1,352	75	5.5	49	7	14.3	2,613	82	3.1
16. Failure to report adverse drug reactions	1,212	0	0.0	1,352	206	15.2	49	9	18.4	2,613	215	8.2
17. Submission of false information	1,212	0	0.0	1,352	0	0.0	49	5	10.2	2,613	5	0.2
18. Other n/a	1,212	0	0.0	1,352	150	11.1	49	16	32.7	2,613	166	6.4
19. Failure to supervise/personally conduct the investigation	1,212	0	0.0	1,352	1	0.1	49	1	2.0	2,613	2	0.1
20. Failure to protect the rights, safety, and welfare of subjects	1,212	0	0.0	1,352	0	0.0	49	2	4.1	2,613	2	0.1
21. Failure to permit FDA access to records	1,212	0	0.0	1,352	0	0.0	49	1	2.0	2,613	1	0.0
Total	*1,212*	*0*	*0.0*	*1,352*	*2,520*	*186.4*	*49*	*166*	*338.8*	*2,613*	*2,686*	*102.8*
For Cause Site Inspection												
01. Records availability	104	0	0.0	332	10	3.0	68	6	8.8	504	16	3.2
02. Failure to obtain and/or document subject consent	104	0	0.0	332	48	14.5	68	15	22.1	504	63	12.5
03. Inadequate informed consent form	104	0	0.0	332	51	15.4	68	15	22.1	504	66	13.1
04. Inadequate drug accountability	104	0	0.0	332	70	21.1	68	28	41.2	504	98	19.4
05. Failure to follow investigational plan	104	0	0.0	332	232	69.9	68	51	75.0	504	283	56.2
06. Inadequate and inaccurate records	104	0	0.0	332	196	59.0	68	50	73.5	504	246	48.8
07. Unapproved concomitant therapy	104	0	0.0	332	8	2.4	68	4	5.9	504	12	2.4
09. Unapproved use of drug before IND submission	104	0	0.0	332	1	0.3	68	2	2.9	504	3	0.6
10. Inappropriate delegation of authority	104	0	0.0	332	11	3.3	68	11	16.2	504	22	4.4
11. Inappropriate use/commercialization of IND	104	0	0.0	332	1	0.3	68	1	1.5	504	2	0.4
12. Failure to list additional investigators on	104	0	0.0	332	9	2.7	68	1	1.5	504	10	2.0
13. Subjects receiving simultaneous investigational drugs	104	0	0.0	332	0	0.0	68	1	1.5	504	1	0.2
14. Failure to obtain or document IRB approval	104	0	0.0	332	21	6.3	68	11	16.2	504	32	6.3
15. Failure to notify IRB of changes/progress reports	104	0	0.0	332	44	13.3	68	9	13.2	504	53	10.5
16. Failure to report adverse drug reactions	104	0	0.0	332	51	15.4	68	13	19.1	504	64	12.7
17. Submission of false information	104	0	0.0	332	5	1.5	68	22	32.4	504	27	5.4
18. Other n/a	104	0	0.0	332	65	19.6	68	29	42.6	504	94	18.7
19. Failure to supervise/personally conduct the investigation	104	0	0.0	332	0	0.0	68	9	13.2	504	9	1.8
20. Failure to protect the rights, safety, and welfare of subjects	104	0	0.0	332	0	0.0	68	7	10.3	504	7	1.4
Total	*104*	*0*	*0.0*	*332*	*823*	*247.9*	*68*	*285*	*419.1*	*504*	*1,108*	*219.8*

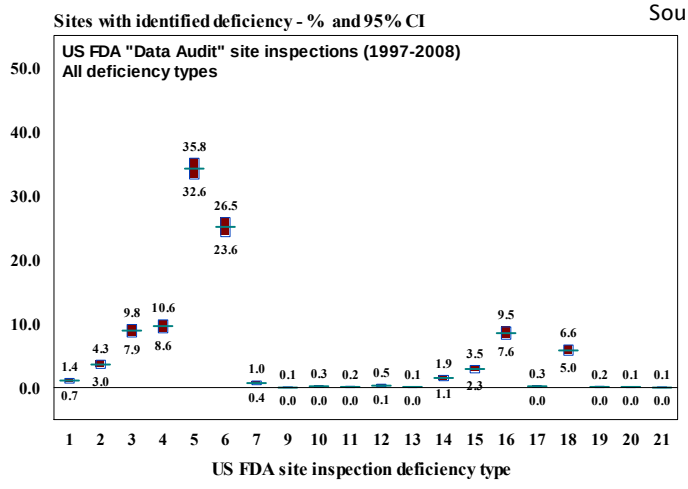

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Figure 10. Proportion - % and 95% confidence interval of the deficiency type findings based on all US FDA Data Audit site inspections globally between 1997 and 2008. Inspection Deficiency Codes in Table 5.

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Table 6. The statistical distribution of the Deficiency Codes following US FDA site inspections between 1997 and 2008 in various geographic regions by the three common Inspection Classification Codes, i.e. No Action, Voluntary Action and Official Action. Values are provided for Data Audit Inspections only.

Data Audit	No Action	Deficiency		Volun-tary Action	Deficiency		Official Action	Deficiency		Total	Deficiency	
Deficiency code	n	n	%	n	n	%	n	n	%	n	n	%
North America												
01. Records availability	1,257	0	0.0	1,405	26	1.9	49	5	10.2	2,711	31	1.1
02. Failure to obtain and/or document subject consent	1,257	0	0.0	1,405	92	6.5	49	10	20.4	2,711	102	3.8
03. Inadequate informed consent form	1,257	0	0.0	1,405	232	16.5	49	14	28.6	2,711	246	9.1
04. Inadequate drug accountability	1,257	0	0.0	1,405	241	17.2	49	15	30.6	2,711	256	9.4
05. Failure to follow investigational plan	1,257	0	0.0	1,405	885	63.0	49	36	73.5	2,711	921	34.0
06. Inadequate and inaccurate records	1,257	0	0.0	1,405	605	43.1	49	38	77.6	2,711	643	23.7
07. Unapproved concomitant therapy	1,257	0	0.0	1,405	20	1.4	49	0	0.0	2,711	20	0.7
09. Unapproved use of drug before IND submission	1,257	0	0.0	1,405	0	0.0	49	1	2.0	2,711	1	0.0
10. Inappropriate delegation of authority	1,257	0	0.0	1,405	4	0.3	49	1	2.0	2,711	5	0.2
11. Inappropriate use/commercialization of IND	1,257	0	0.0	1,405	3	0.2	49	0	0.0	2,711	3	0.1
12. Failure to list additional investigators	1,257	0	0.0	1,405	10	0.7	49	0	0.0	2,711	10	0.4
13. Subjects receiving simultaneous investigational drugs	1,257	0	0.0	1,405	2	0.1	49	0	0.0	2,711	2	0.1
14. Failure to obtain or document IRB approval	1,257	0	0.0	1,405	39	2.8	49	5	10.2	2,711	44	1.6
15. Failure to notify IRB of changes/progress reports	1,257	0	0.0	1,405	76	5.4	49	7	14.3	2,711	83	3.1
16. Failure to report adverse drug reactions	1,257	0	0.0	1,405	213	15.2	49	9	18.4	2,711	222	8.2
17. Submission of false information	1,257	0	0.0	1,405	0	0.0	49	5	10.2	2,711	5	0.2
18. Other n/a	1,257	0	0.0	1,405	151	10.7	49	16	32.7	2,711	167	6.2
19. Failure to supervise/personally conduct the investigation	1,257	0	0.0	1,405	1	0.1	49	1	2.0	2,711	2	0.1
20. Failure to protect the rights, safety, and welfare of subjects	1,257	0	0.0	1,405	0	0.0	49	2	4.1	2,711	2	0.1
21. Failure to permit FDA access to records	1,257	0	0.0	1,405	0	0.0	49	1	2.0	2,711	1	0.0
Total	*1,257*	*0*	*0.0*	*1,405*	*2,600*	*185.1*	*49*	*166*	*338.8*	*2,711*	*2,766*	*102.0*
Latin America												
01. Records availability	35	0	0.0	44	1	2.3	2	0	0.0	81	1	1.2
02. Failure to obtain and/or document subject consent	35	0	0.0	44	2	4.5	2	2	100.0	81	4	4.9
03. Inadequate informed consent form	35	0	0.0	44	3	6.8	2	0	0.0	81	3	3.7
04. Inadequate drug accountability	35	0	0.0	44	4	9.1	2	1	50.0	81	5	6.2
05. Failure to follow investigational plan	35	0	0.0	44	28	63.6	2	2	100.0	81	30	37.0
06. Inadequate and inaccurate records	35	0	0.0	44	25	56.8	2	2	100.0	81	27	33.3
15. Failure to notify IRB of changes/progress reports	35	0	0.0	44	3	6.8	2	0	0.0	81	3	3.7
16. Failure to report adverse drug reactions	35	0	0.0	44	9	20.5	2	0	0.0	81	9	11.1
18. Other n/a	35	0	0.0	44	1	2.3	2	0	0.0	81	1	1.2
Total	*35*	*0*	*0.0*	*44*	*76*	*172.7*	*2*	*219*	*350.0*	*81*	*83*	*102.5*
Europe												
01. Records availability	116	0	0.0	161	0	0.0	10	1	10.0	287	1	0.3
02. Failure to obtain and/or document subject consent	116	0	0.0	161	9	5.6	10	1	10.0	287	10	3.5
03. Inadequate informed consent form	116	0	0.0	161	28	17.4	10	4	40.0	287	32	11.1
04. Inadequate drug accountability	116	0	0.0	161	32	19.9	10	7	70.0	287	39	13.6
05. Failure to follow investigational plan	116	0	0.0	161	117	72.7	10	8	80.0	287	125	43.6
06. Inadequate and inaccurate records	116	0	0.0	161	88	54.7	10	10	100.0	287	98	34.1
07. Unapproved concomitant therapy	116	0	0.0	161	4	2.5	10	0	0.0	287	4	1.4
14. Failure to obtain or document IRB approval	116	0	0.0	161	1	0.6	10	0	0.0	287	1	0.3
15. Failure to notify IRB of changes/progress reports	116	0	0.0	161	4	2.5	10	0	0.0	287	4	1.4
16. Failure to report adverse drug reactions	116	0	0.0	161	37	23.0	10	0	0.0	287	37	12.9
18. Other n/a	116	0	0.0	161	16	9.9	10	5	50.0	287	21	7.3
19. Failure to supervise/personally conduct the investigation	116	0	0.0	161	1	0.6	10	0	0.0	287	1	0.3
Total	*116*	*0*	*0.0*	*161*	*337*	*209.3*	*10*	*36*	*300.0*	*287*	*373*	*130.0*

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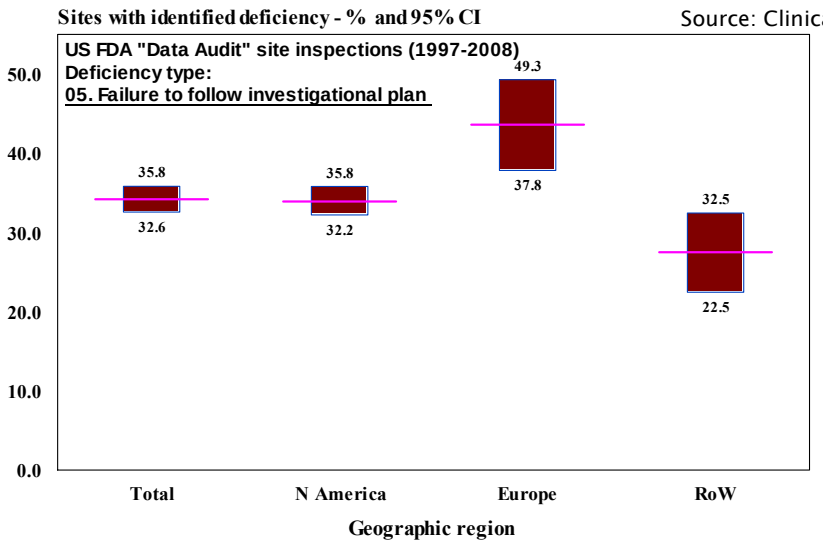
Table 6. (Continuation) The statistical distribution of the Deficiency Codes following US FDA site inspections between 1997 and 2008 in various geographic regions by the three common Inspection Classification Codes, i.e. No Action, Voluntary Action and Official Action. Values are provided for Data Audit Inspections only.

Data Audit	No Action	Deficiency		Volun-tary Action	Deficiency		Official Action	Deficiency		Total	Deficiency	
Deficiency code	n	n	%	n	n	%	n	n	%	n	n	%
East Europe												
01. Records availability	74	0	0.0	74	2	2.7	2	0	0.0	150	2	1.3
02. Failure to obtain and/or document subject consent	74	0	0.0	74	3	4.1	2	0	0.0	150	3	2.0
03. Inadequate informed consent form	74	0	0.0	74	5	6.8	2	0	0.0	150	5	3.3
04. Inadequate drug accountability	74	0	0.0	74	6	8.1	2	1	50.0	150	7	4.7
05. Failure to follow investigational plan	74	0	0.0	74	34	45.9	2	1	50.0	150	35	23.3
06. Inadequate and inaccurate records	74	0	0.0	74	40	54.1	2	1	50.0	150	41	27.3
15. Failure to notify IRB of changes/progress reports	74	0	0.0	74	3	4.1	2	0	0.0	150	3	2.0
16. Failure to report adverse drug reactions	74	0	0.0	74	7	9.5	2	0	0.0	150	7	4.7
18. Other n/a	74	0	0.0	74	3	4.1	2	0	0.0	150	3	2.0
Total	*74*	*0*	*0.0*	*74*	*103*	*139.2*	*2*	*3*	*150.0*	*150*	*106*	*70.7*
Middle East												
05. Failure to follow investigational plan	0	0	0.0	1	1	100.0	0	0	0.0	1	1	100.0
06. Inadequate and inaccurate records	0	0	0.0	1	1	100.0	0	0	0.0	1	1	100.0
Total	*0*	*0*	*0.0*	*1*	*2*	*200.0*	*0*	*0*	*250.0*	*1*	*2*	*200.0*
Africa												
02. Failure to obtain and/or document subject consent	18	0	0.0	12	1	8.3	1	0	0.0	31	1	3.2
03. Inadequate informed consent form	18	0	0.0	12	4	33.3	1	0	0.0	31	4	12.9
04. Inadequate drug accountability	18	0	0.0	12	1	8.3	1	0	0.0	31	1	3.2
05. Failure to follow investigational plan	18	0	0.0	12	8	66.7	1	0	0.0	31	8	25.8
06. Inadequate and inaccurate records	18	0	0.0	12	3	25.0	1	1	100.0	31	4	12.9
14. Failure to obtain or document IRB approval	18	0	0.0	12	3	25.0	1	0	0.0	31	3	9.7
16. Failure to report adverse drug reactions	18	0	0.0	12	1	8.3	1	0	0.0	31	1	3.2
Total	*18*	*0*	*0.0*	*12*	*21*	*175.0*	*1*	*1*	*350.0*	*31*	*22*	*71.0*
Asia												
03. Inadequate informed consent form	15	0	0.0	21	3	14.3	0	0	0.0	36	3	8.3
04. Inadequate drug accountability	15	0	0.0	21	8	38.1	0	0	0.0	36	8	22.2
05. Failure to follow investigational plan	15	0	0.0	21	6	28.6	0	0	0.0	36	6	16.7
06. Inadequate and inaccurate records	15	0	0.0	21	13	61.9	0	0	0.0	36	13	36.1
12. Failure to list additional investigators on	15	0	0.0	21	1	4.8	0	0	0.0	36	1	2.8
14. Failure to obtain or document IRB approval	15	0	0.0	21	1	4.8	0	0	0.0	36	1	2.8
15. Failure to notify IRB of changes/progress reports	15	0	0.0	21	2	9.5	0	0	0.0	36	2	5.6
16. Failure to report adverse drug reactions	15	0	0.0	21	4	19.0	0	0	0.0	36	4	11.1
18. Other n/a	15	0	0.0	21	1	4.8	0	0	0.0	36	1	2.8
Total	*15*	*0*	*0.0*	*21*	*39*	*185.7*	*0*	*0*	*0.0*	*36*	*39*	*108.3*
Oceania												
05. Failure to follow investigational plan	3	0	0.0	4	4	100.0	0	0	0.0	7	4	57.1
06. Inadequate and inaccurate records	3	0	0.0	4	1	25.0	0	0	0.0	7	1	14.3
16. Failure to report adverse drug reactions	3	0	0.0	4	1	25.0	0	0	0.0	7	1	14.3
Total	*3*	*0*	*0.0*	*4*	*6*	*150.0*	*0*	*0*	*0.0*	*7*	*6*	*85.7*



Source: Clinical Trial Magnifier Vol. 2:4 Apr 2009
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Figure 11a. Proportion - % and 95% confidence interval - of FAILURE TO FOLLOW INVESTIGATIONAL PLAN deficiency type findings based on all US FDA Data Audit site inspections between 1997 and 2008 by geographical representativeness.

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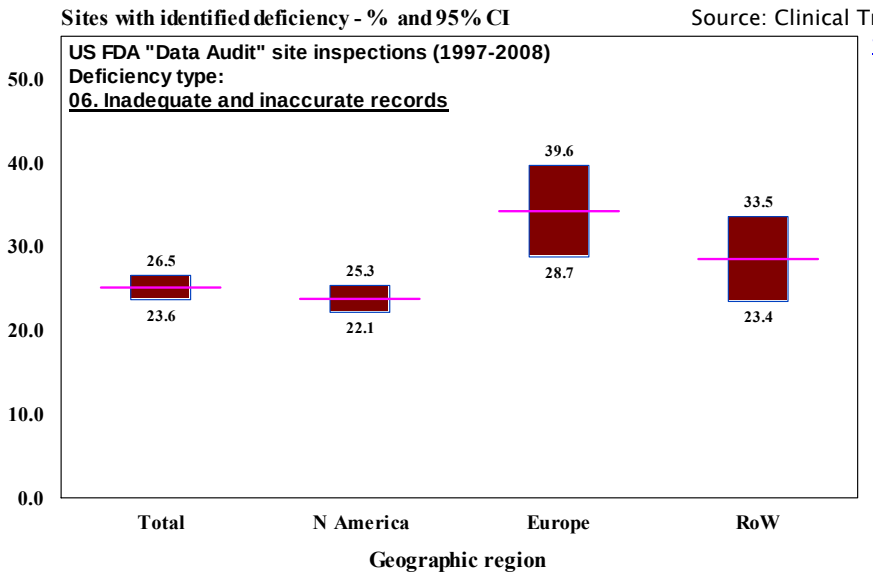
Discussion

This study convincingly shows a significant geographic difference in deficiency findings identified during US FDA Data Audit clinical trial site inspections. Rest-of-the-world has in general somewhat better inspection results than North America, which in turn has somewhat better results than Europe. East Europe, with 150 completed inspections, has in fact the best overall results – with just 3.3% of its site inspections having three or more deficiencies, compared to 20.2% of sites in Europe.

In line with previous studies, the most common deficiencies identified are "Failure to follow investigational plan" (34.2%), "Inadequate and inaccurate records" (25.1%), "Inadequate drug accountability" (9.6%), "Inadequate informed consent form" (8.9%) and "Failure to report adverse drug reactions" (8.5%).[4] However, there are also geographic differences. A relatively higher number of deficiencies is reported for European sites, such as 43.6% for "Failure to follow investigational plan", compared with 33.9% for North America ($p<0.05$) and 27.5% ($p<0.05$) for RoW. In Europe, 34.2% of all inspections reported "Inadequate and inaccurate records", compared with 23.7% for North America ($p<0.05$) and 28.5% ($p>0.05$) for RoW. "Inadequate



Source: Clinical Trial Magnifier Vol. 2:4 Apr 2009
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Figure 11b. Proportion – % and 95% confidence interval – of INADEQUATE AND INACCURATE RECORDS deficiency type findings based on all US FDA Data Audit site inspections between 1997 and 2008 by geographical representativeness.

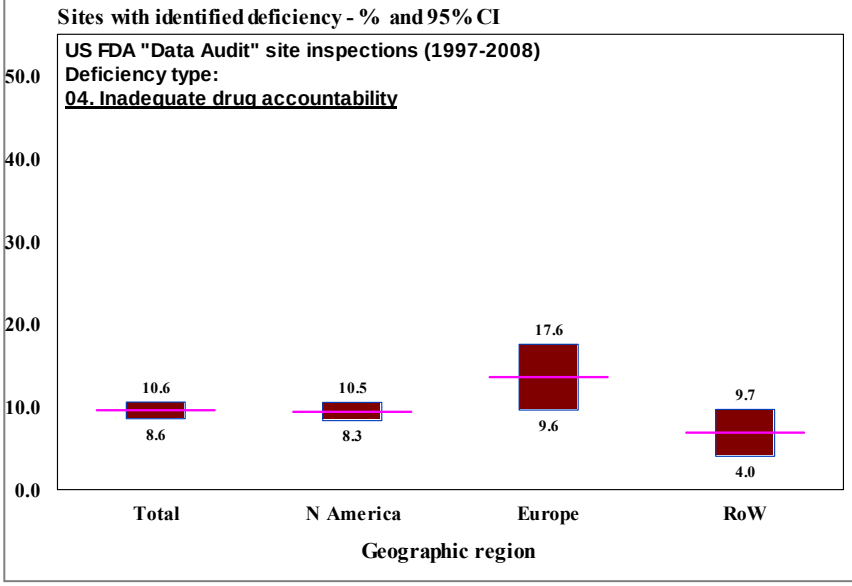

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Figure 11c. Proportion – % and 95% confidence interval – of INADEQUATE DRUG ACCOUNTABILITY deficiency type findings based on all US FDA Data Audit site inspections between 1997 and 2008 by geographical representativeness.

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informed consent form" was found in 4.9% of RoW inspections ($p<0.05$), as compared to 9.1% in North America and 11.1% in Europe.

Other observations, though not always statistically significant, point in the same direction. For example, 3.5% of inspections in Europe prompted Official Action, compared to 1.8% in North America and 1.6% in RoW. Over the 12 years of inspections, 49 Official Actions were in North America, 10 in Europe, two in Latin America, two in East Europe and one in Africa – but none in the Middle East, Asia or Oceania.

Submitting false information is certainly the most serious violation in a sponsored trial and virtually always related to financial benefits, namely fabricated patients and/or patient data or violation of inclusion/exclusion criteria. Among the routine Data Audit inspections between 1997 and 2008 were five inspections identified with submission of false information. They were all in the US, and all resulted in Official Action. Virtually all For Cause inspections are in the US. Among those, 27 identified submission of false information and 22 led to Official Action. No inspection outside the US reported submission of false information.

As a result of the globalization of industry sponsored clinical trials, the number of US FDA site inspection outside the US and Europe has increased steadily over the past decade. Between 2003–2008 there were 233 site

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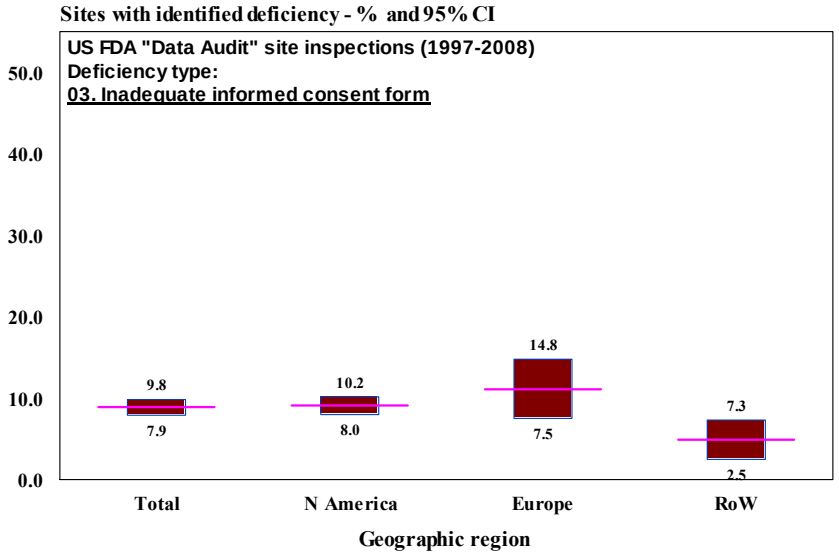

Figure 11d. Proportion – % and 95% confidence interval – of INADEQUATE INFORMED CONSENT FORM deficiency type findings based on all US FDA Data Audit site inspections between 1997 and 2008 by geographical representativeness.

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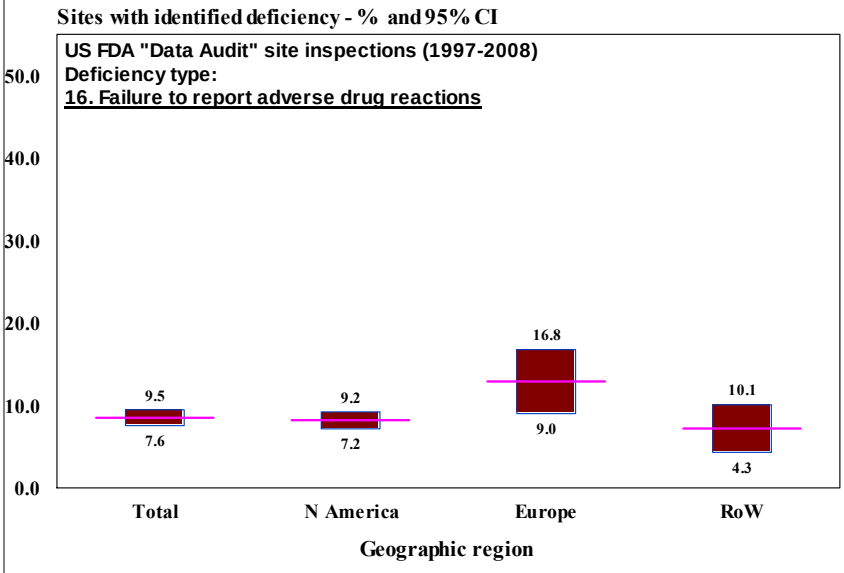

Figure 11e. Proportion – % and 95% confidence interval – of FAILURE TO REPORT ADVERSE DRUG REACTIONS deficiency type findings based on all US FDA Data Audit site inspections between 1997 and 2008 by geographical representativeness.

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inspections in the RoW, compared with 128 in Europe and 1,218 in North America. It is not clear why inspections have decreased in Europe and increased in RoW. It cannot reflect past inspection results, since the RoW clearly scores better overall than Europe. However, it may be because the number of trial subjects is higher at RoW sites than in Europe, thus attaching to them more importance in new drug applications.

FDA's oversight of clinical trials

The Department of Health and Human Services, Office of Inspector General published a 2007 report entitled "The Food and Drug Administration's Oversight of Clinical Trials".[8] This report aimed to determine the extent to which the US FDA conducted inspections of clinical trials from fiscal year 2000 to 2005, and assess its inspection processes. The report's findings are as follows:

- Data limitations inhibit FDA's ability to effectively manage the BiMo program. Because FDA does not maintain a clinical trial registry, it is unable to identify all ongoing clinical trials and their associated trial sites. Further, because FDA does not maintain an IRB registry, it is unable to identify all IRBs.
- Other factors hinder FDA's ability to effectively manage the BiMo program; Centers and ORA inconsistently classify OAI and NAI inspections. FDA relies on voluntary compliance to correct violations of regulatory significance.
- It is estimated that FDA inspected 1 percent of clinical trial sites during the fiscal year 2000–2005 period. FDA conducted 2,856 BiMo inspections that required a clinical trial site visit during the FY 2000–2005 period. The centers conduct more inspections that verify clinical trial data than inspections that focus on human subject protections. Seventy-five percent of the BiMo inspections during the FY 2000–2005 period were surveillance inspections, which generally target previously completed trials and often focus on verifying the quality of clinical trial data.

The report made the following recommendations for improving information systems and processes:

- Develop a clinical trial database that includes all clinical trials. FDA should develop a comprehensive internal database of clinical trials to more effectively identify and target ongoing clinical trials for inspection.
- Create an IRB registry. This registry would give FDA basic information about IRBs that it now lacks. By identifying all IRBs overseeing clinical trials, FDA could target IRBs more effectively for inspection.
- Create a cross-center database that allows complete tracking of BiMo inspections. A database that includes timely and complete information about all BiMo inspections would help FDA better coordinate and track inspections.
- Establish a mechanism to provide feedback to BiMo investigators on their inspection reports and findings. Improved feedback between the centers and BiMo investigators could lead to a common understanding of the regulations and

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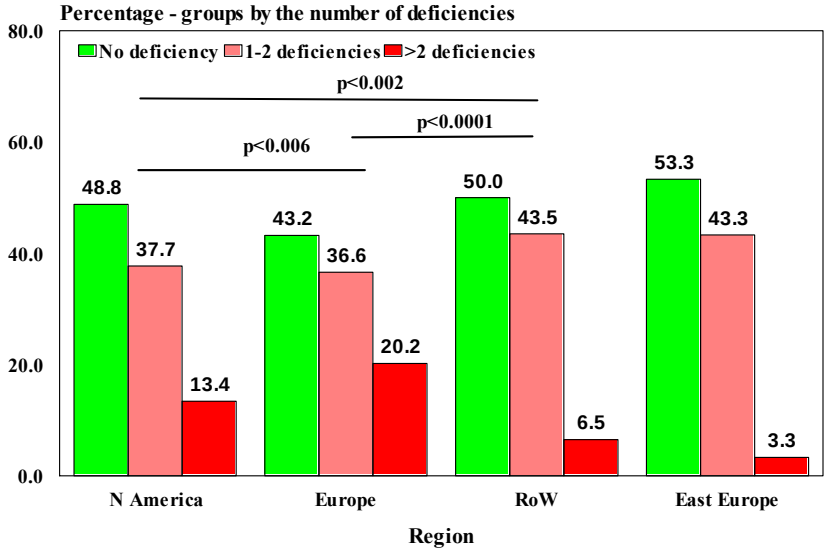

Figure 12. Proportion (%) of the number of sites inspected with no deficiency, 1–2 or over 2 deficiencies for all US FDA Data Audit site inspections between 1997 and 2008. A 3*2 Chi-Square test has been applied. Values not given in Table.

guidelines that govern BiMo inspections.

- Seek legal authority to provide oversight that reflects current clinical trial practices. FDA should consider seeking additional authority that covers all of the stakeholders in the management and conduct of clinical trials. In particular, FDA could seek to expand its authority to include the colleagues and subordinates of a clinical investigator if they participate in the conduct of a clinical trial.

In short, the report disclosed that federal health officials did not know how many clinical trials were being conducted, audited fewer than one per cent of testing sites and, on the rare occasions when inspectors did appear, generally showed up long after tests had been completed. The US FDA has about 200 inspectors keeping watch over an estimated 350,000 testing sites. Even when the inspectors found serious problems in clinical trials, senior FDA officials downgraded the findings 68 per cent of the time. Among the remaining cases, the agency almost never followed up with inspections to determine whether corrective actions the agency demanded had been implemented.

In light of this, one can argue that the US FDA does not perform its site inspections efficiently, and that not enough site inspections are conducted. There is seemingly also administrative deficiency in documentation and follow-up of inspections. However, the US FDA is still unique in making all inspection reports publicly available; and is in our view as such the only regulatory body worldwide providing access to such important information. In fact, it is the only solid reliable information source currently available to attempt to determine global research standards.

Accelerate recruitment

A main reason for going global is to shorten the timeline for clinical testing.[3] Surely, this is the most common and important reason for conducting clinical trials in emerging locations. There is a tough competition between pharmaceutical companies in identifying sites and patients in North America and Western Europe. Large, emerging countries offer fast subject recruitment rate, significantly accelerating the clinical development programme. Earlier regulatory approval of a new medicinal product – even by a few months – can clearly impact the total revenue for a company, due to the patent duration deadline.

Uninterrupted globalization of clinical trials

In a previous *Magnifier* article we depicted ongoing globalization of clinical trials and showed the relative change among the 30 most active trial countries.[9] Countries with the largest growth in proportion of all sites over the past 15 months are Russia, India, Japan, Brazil and Ukraine. The ten countries with the lowest growth are all in North America and Western Europe – with the US, UK and Canada at the lower end. There are some changes in ranking between the top 30 countries. Virtually all RoW countries are moving up the ladder. Japan is up from 8th to 5th place and all four BRIC countries are improving in ranking, although China remains outside the top 20. Russia is now 9th (from 10th), India is 12th (from 18th) and Brazil is 14th (from 20th).[16]

The industry clearly continues to move more and more study sites to emerging regions due to the lack of

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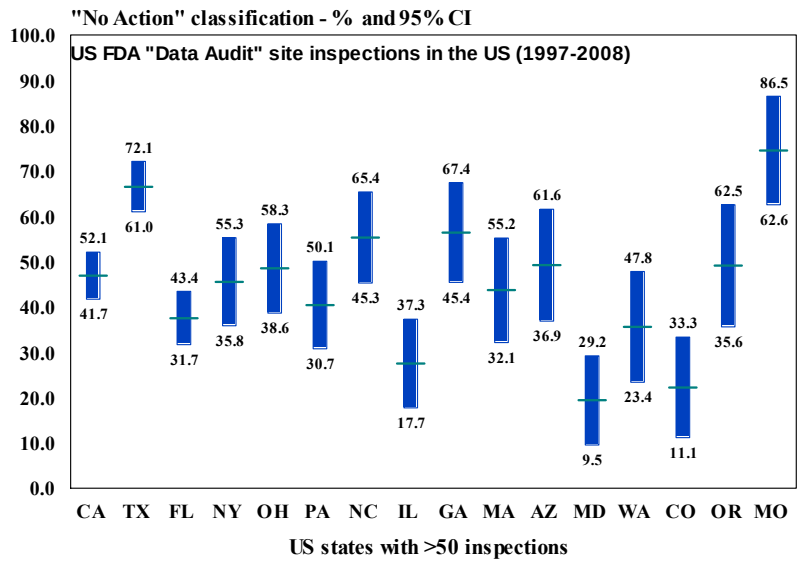

Figure 13. Proportion – % and 95% confidence interval – of No Action classification for US FDA Data Audit site inspections between 1997 and 2008 in US States with over 50 such inspections. Values not given in Table.

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enough investigators and subjects in the established regions. If the quality of the data collected in emerging regions was a major concern they would not be a part of the rapid globalization of clinical research. Such concerns are also not supported by the large number of US site inspections been conducted over the past 12 years as demonstrated in this study.

Conclusion

As we report, East Europe, with 150 completed US FDA inspections, has the best overall results, with 3.3% of its site inspections having three or more deficiencies, compared with 20.2% in Europe. A significant, relatively higher number of deficiencies are also reported for European sites, notably 43.6% for "Failure to follow investigational plan", compared with 33.9% for North America and 27.5% for RoW. It is therefore ironic that the European Medicines Agency (EMEA) recently posted a strategy paper expressing growing concern about how well clinical trials are conducted from an ethical and scientific standpoint in regions outside Europe and North America, namely Africa, Asia, Latin America and Russia. Our findings strongly imply that equal or even stronger concerns should be directed towards Western European investigator sites.

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Subscriber letter

Dear Editor,

It would be nice to see someone address the issue of Phase I healthy subjects and how this has turned into a profession for them. It would be advantageous for all phases of a drug trial to be conducted within the proposed targeted therapeutic population. It is my belief that by limiting participation, the industry will see a sharp decline in AE reporting. Furthermore, it is my belief that only then will the actual efficacy of a drug truly be known.

The conduct of clinical research trials should come under the guidance and regulation of a global regulatory agency, funded in part by all countries involved in clinical research trials and by the pharmaceutical companies. Moreover, the Principal Investigators should no longer be the sole individual held responsible for the conduct of a clinical trial; all clinical research staff should be held just as accountable for the conduct of the trial. It is my firm belief that each research professional be responsible for his or her part in the trial alongside the PI of record. This is another area that if regulated more closely would produce cleaner and more accurate data and the integrity would be less compromised.

It would be most interesting to view the results of an overall survey addressing the above mentioned issues faced within the clinical trial industry on a global level.

Thank you for taking the time to review this email; please feel free to contact me with any questions or concerns you may have.

Sincerely,

Astrid C. Cruz, CCRC

Contract Clinical Trials Site Manager, Palm Coast, Florida USA

Dear Astrid C. Cruz,

Thank you for the comments. I fully agree with the points that you are making in relation to Phase I trials; especially that more patients should be studies rather than healthy volunteers.

With the best regards

Johan Karlberg, MD, PhD

Subscriber letter

Dear Dr. Karlberg,

Greetings from Iran. I would be interested to join the *Magnifier's* advisory group.

I act as the consumer coordinator for the Iranian Cochrane Information Network (ICInet). ICInet is a network of Iranian Cochrane contributors working with the UK Cochrane Centre under the direction of Dr. Mona Nasser.

We provide consumer peer reviews for Cochrane reviews which are systematic reviews of health care interventions and are largely based on Randomized controlled trials and Controlled clinical trials and we are interested to find ways to increase the involvement of consumers and patients in the design and planning of RCTs, especially in selecting patient relevant outcomes that are relevant not only to patients in developed countries but also developing countries.

I would also recommend my two colleagues, Hoda Javaheri, who is closely working with me on the consumer coordination, and Dr. Maryam Shahiri, who is the hand searching program coordinator of the ICInet. The hand searching program is an international program across the Cochrane Collaboration on hand searching medical and health care journals to identify clinical trials that are not identified through searching databases (for reasons like lack of indexing).

Kobra Yassini (BSc) and Hoda Javaheri (MSc)

Consumer Coordinators, The Iranian Cochrane Informal Network (www.dent.sbmu.ac.ir/icinet.asp)

Best Regards,

Dear Kobra Yassini and Hova Javaheri,

Thank you for the note. We will add your name and your college's name to the Advisory Committee Members. However, we need to collect some additional information, so we will be in contact with you in a short while.

With the best regards

Johan Karlberg, MD, PhD

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Commentary to "Emerging Queries on the Legitimacy and Validity of Globalization of Clinical Trials".

By Maxim Belotserkovsky, MD, DS

PSI Co Ltd, St. Petersburg, Russia

Dear Johan,

I am sorry for sending you rather extended commentary on your very interesting article.[1] I simply would like to add some spice and salt to the discussion and point out that there is some ground around all this discussion about acceptability of the clinical data from developing countries.

I'm sure that when you know the diagnosis you may use the right remedy and overcome a problem.

Regards,

Maxim

Patient Patterns and Globalization of Clinical Trials

I would like to emphasize the fact that both American and European regulatory authority representatives and reputed scientists and physicians more and more frequently criticize the data received during clinical trials in the developing world. Allowing for the fact that more than 90 % of drugs are created with the money of American, Western European and Japanese investors, and 90 % of drug sales profit comes from American, Western European and Japanese markets, we should admit that the bigger part of clinical research is conducted to get drugs registered in the developed countries. Because of this, regardless of the country of origin of the medical data, these data should primarily be convincing to regulators in the US, Western Europe, and Japan.

We may regard these voices against globalization of clinical trials process as a possible protest by patriots of these countries against money leaving their countries. But even if this motive is present, I am absolutely sure it's not the principal one. The principal one is medical concern that data obtained in developing countries may be reproduced for the treatment of patients in developing countries. In other words, will the medications proved to effectively treat patients in developing countries be as effective to treat patients in the developed world?

I would like to provide five different examples where in different parts of the world patients with the same diagnosis, and consequently formally eligible for entry criteria, actually represent completely different patterns:

Antibacterial resistance

It's commonly known that when penicillin was first invented, it was sufficient to administer 50,000-100,000 units of penicillin 3-4 times a day to heal wound infections during World War II. In the rare cases when penicillin is prescribed today, dosage may be up to 12-20 million units up to 6 times a day, yet considered of little effectiveness. Bacteria have become resistant to this antibiotic. Unfortunately, as we all know, resistance develops to absolutely all antibiotics, which spurs the development of more and more powerful drugs.

It's well known that the highest level of antibacterial resistance is registered in the US (specifically, frequency of MRSA (Methycillin-Resistant Staphyloccocus Aureus), VISA (Vancomycyn Intermediate Susceptible Staphyloccocus Aureus), VRSA (Vancomycin-Resistant Staphyloccocus Aurea), PRP level (Penicyllin Resistant Pneumococci), and VRE (Vancomycin-Resistant Enterococci) levels, etc.). While, for instance, in Finland, Sweden, Denmark and Norway the level of antibacterial resistance is low. Therefore, if we are going to test a particular antibacterial molecule in such countries with low antibacterial resistance, these data may not be automatically extended to assume the effectiveness of this drug in the US. At the same time, if a drug proves effective in a country with highest antibacterial resistance (particularly the USA), it would also work in countries with more favorable antibacterial resistance landscape.

Viruses also have a capacity to develop resistance to anti-viral medicines. For example, it is well known that when treating with Lamivudin, the Hepatitis B virus (HBV) develops resistance to this drug, and the more exposition, the more the resistance. In countries where Lamivudin is standard therapy, the Hepatitis B virus resistance to it is more and more frequently observed in patients who have never received Lamivudin. It is an analogous situation to that of antibacterial resistance.

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Difference in patterns due to under standard treatment of frequent diseases in developing countries.

If we take the problem of congestive heart failure (CHF), we see that the patient pool in different countries consists of patients with different patterns of CHF.

In the US and the developed countries CHF patients are predominantly aged people with Hypertension and Diabetes Mellitus-II, among whom women are somehow prevailing. While in the developing countries, the majority of the CHF patients are male with under standard (compared to the developed countries) prior treatment of Ischemic Heart Disease, leading to aneurism and other complications of Acute Myocardial Infarction, i.e. the syndrome of CHF is the same, but the patient pool is different and thus the results of therapy may differ as well.

Difference in patterns of the pretreatment of patients

Many studies in inflammatory bowel disease (Crohn's disease and ulcerative colitis) observed significant difference in the results of treating patients in developed countries vs. developing countries. The analysis of patient pool shows that an average patient enrolled into a study from the developed world has a history of 6-8 years of treatment, having received 3-5 different regimens of therapy. Yet patients from the developing countries in most cases have a history of 2-4 years and 2-3 treatment regimens.

The reason for these differences is self-evident, due to the iniquity of access to standard therapy in different parts of the world. Patients from the developed world have access to more treatment modalities and are treated in accordance with available "standard" treatment modalities 2-3 times longer. Please note that the disease is called inflammatory bowel disease, which means that the basis of this disease is a typical pathological process of chronic inflammation. Each sophomore of each Medical School should be aware that the result of inflammation (especially chronic) is always sclerosis and fibrosis.

This way, a patient with a badly controlled disease and history of 8 years has a much higher level of both sclerosis and fibrosis in gut, and thus the possibility to improve bowel function is much lower for patients in the developing countries than for patients in developed countries. I am not saying this is either good or bad. I am just saying they should have different response to therapy expected. This may subsequently lead to a problem of interpreting the overall study data, and consequently serious discussion among regulatory bodies and the medical society.

Acute myeloid leukemia

In developing countries and the developed world the diagnosis is absolutely the same, but patient patterns may be also rather different. The reason is also the general quality of healthcare, in this case, for aged patients and those with multiple co-morbidities. In other words, the patients that would not survive until the point where acute myeloid leukemia develops and die earlier due to different malignancies and other complications will be a majority in the developing countries. Thus, the diagnosis is the same, but the patient patterns are really different. Any doctor knows that co-morbidities must be seriously considered when selecting the treatment tactics.

Pretreatment in oncology trials related to available standard best supportive care and rescue medication

Oncology patients in developed countries undergo treatment benefiting from higher standards of best supportive care and much higher availability of rescue medication. As a result they often receive higher doses of chemotherapy and more intensive and/or longer courses of chemotherapy, just because there is the possibility to prevent and cure possible complications. So, they are able to undergo more aggressive therapy. The diagnosis is the same and pretreatment is the same (formally), but patterns of patients may differ.

I could go on with list quite easily, but it seems to me that the above examples demonstrate that the problem of patient patterns heterogeneity in the developed and developing countries cannot be overlooked. But as a medical doctor, after diagnosing a patient I must automatically consider the further treatment.

Conclusions

- The difference in treatment standards, accessibility of treatment, healthcare, complications management, etc. should always be taken into consideration when planning a study. This is why conducting a study in what we call the rest of the world requires higher medical supervision at the stage of planning and all subsequent stages of the study.

- If a study is not focused on registered the study drug in a particular country in a different part of the world, study protocols should be much more specific in detailing entry criteria for those patient

patterns that are fit for the US and the Western countries to be enrolled in the study.

- Wider use of stratifying patients in clinical protocols will allow maintaining the proportion of patients with the different patterns of the same disease that would be convincing for the regulators, who will subsequently register the medication in question.

I realize that these remedies may decrease enrolment rates in the developing countries in many indications, but in my opinion this is the only way to ensure the sustained globalization of clinical trials.

I should also stress that we use/promulgate this attitude towards different patterns of patients in different indications. Use of this approach, including intensive medical supervision running clinical studies in developing countries, helps us not only enroll fast, but also generate quality and convincing data. Currently, our company is proud of eight medicines registered by FDA, with more than 50% of pivotal data from developing countries.

While preparing this summary (commentary), I used my personal experience and the experience of my medical school classmate Dr. Nickolai Usachev, MD, PhD.

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Dear Maxim,

I highly appreciate your commentary and completely agree that the variation in medical practice between countries/regions can influence the results of a clinical trial, both by means of efficacy and adverse events reaction observations.

The vast majority of early phase trial – phase I and II – are still conducted in the established regions, which means that the initial safety profile and proof-of-concept studies are predominantly made in the regions where the medicinal products primarily are to be filed. Those trials are thus assumed to be made in an environment where similar or close to medical practices rule.

The large scale phase III trials are however more global in nature. Since those trials are large scaled it would not be difficult to conduct sub-group analysis of the data by geographic region to establish any differences in the efficacy and safety outcomes. Identified differences should be addressed and made publicly available, since they can be related to both extrinsic and intrinsic factors also of importance for populations outside the established regions.

The dialogue on this issue should be focused, sound and supported by valid data such as the case is with your commentary.

However, the general opinion put forth in the West that clinical studies conducted in emerging regions are of poor quality and unethical has little warranty. In this *Magnifier* issue we in fact highlight this by analyzing US FDA site inspection data, which clearly implies that Western Europe and to some extent North America have more negative site inspection findings than the rest-of-the-world.

The discussion should thus be focused on the scientific rationale behind trials conducted in established and emerging regions, and not on other aspects that are not as yet proven to be relevant.

You mentioned that "We may regard these voices against globalization of clinical trials process as possible protest by patriots of their countries against money leaving their countries." This might be true, but the multinational pharmaceutical industry's primary concern is to have the "business done" in a promptly manner, be it in established or emerging regions, as long as the sites can deliver in time and that the data is valid. If the established regions met the needs of the industry we would not have this debate – at least not until the emerging regions become a main target for drug development and the market attention.

With the best regards

Johan Karlberg, MD, PhD

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Track: Keynote & Plenary	
Keynote address: Clinical research in Malaysia	Tan Sri Dato' Seri Hj Dr Mohd Ismail Merican Director-General of Health Malaysia
Plenary: Regulations & MOH guidelines for clinical research	Datuk Dr Maimunah A Hamid Deputy Director- General of Health (R&TS) MOH
Plenary: Issues and challenges facing the global development of new medicines	Prof Nadarajah Sreeharan Professor of Post Graduate Med School, University of Surrey, UK
Track: Clinical research in Malaysia	
The MOH Research Ethics Committee	Dr Chang Kian Meng Chair, Medical Research Ethics Committee
Funding for clinical research in financially challenging times	Dr S. Asmaliza Secretariat NIH/MREC
Regulation of ethics committees in Malaysia	Dr Kamaruzaman Saleh Head of Clinical Research & Compliance Section, National Pharmaceutical Control Bureau, MOH
Role of CIC in promoting clinical research in UMMC	Prof Dr Rosmawati Mohamed University Malaya Medical Centre UMMC
Role of CRC in promoting clinical research in HUSM	Prof Dr Nor Hayati Othman Dean (Clinical Research Platform) Universiti Sains Malaysia
Role of CRC in promoting clinical research in UKMMC	Prof Dr Rohaizak Muhammad Deputy Dean of Research and Industry UKMMC, Chair UKM ethics committee
Conducting clinical trial in Malaysia: Pharma sponsors' experience	Dr Bernard Ng Medical Director, Sanofi Aventis

Track: CRO industry in Malaysia	
Role of CRC in promoting Malaysia to industry	Dr Ong Loke Meng Head of CRC Hospital Pulau Pinang
Development of the CRO industry in Malaysia	Mr Selvam Ramaraj Senior VP Healthcare, BiotechCorp Malaysia
Clinical Research Outsourcing: Opportunities and challenges	Dr Anand Tharmaratnam CEO Quintiles SE Asia
Track: Drug development	
Cancer genomics, biomarkers & drug development	Dr Teo Soo-Hwang Chief Executive, Cancer Research Initiatives Foundation, CARIF
Virtual drug development	Dr Christo van Niekerk CEO Global Alliance for TB Drug Development
Early phase studies: Does Malaysia have a chance?	Dr Maurice Cross Director, Veeda Clinical Research UK
International GLP standards	Dr Kumar Kurumaddali Malladi India
Tissue banking & drug development	Dr Matthew Lear Director of Strategic Alliances, Asterand US
Track: Off the beaten path	
Breast cancer research	Prof Yip Cheng Har Consultant in General and Breast Surgery, UMMC
Paediatric clinical trial in Malaysia	Dato' Dr Jimmy Lee Kok Foo Head of CRC Terengganu
Medical device epidemiology & Malaysian statistics on medical device	Zamane Abdul Rahman Director Medical Device Buraeu MOH Chairman NMDS

PRE-CONFERENCE WORKSHOPS

#	DATE	WORKSHOP/ SEMINAR/ EVENT
1.	8 JULY (5-7PM)	AGM ACRP MALAYSIAN CHAPTER
2.	9 JULY 5-7PM	MID-YEAR DIALOGUE WITH INDUSTRY SPONSORS FOR CLINICAL TRIAL
3.	8 JULY	FORUM FOR ETHICS REVIEW COMMITTEES IN MALAYSIA (FERCIM) CUM CONTINUING EDUCATION ON RESEARCH ETHICS
4.	7-8 JULY	ACRP MALAYSIAN CHAPTER'S TRAINING COURSES FOR CRAS AND SCS
5.	6-8 JULY	GCP WORKSHOP
6.	7-8 JULY	ADVANCED GCP WORKSHOP
7.	6 JULY	PHARMACEUTICAL MEDICINE SEMINAR: PLANTS TO MEDICINES
8.	6 JULY	RESEARCH, PUBLICATIONS & CITATIONS
9.	6 JULY	DRUGS FOR NEGLECTED DISEASES
10.	7 JULY	PHARMACEUTICAL MEDICINE SEMINAR: MOLECULES TO MEDICINES"
11.	7 JULY	PHARMACO-ECONOMICS
12.	8 JULY	HEALTHCARE ECONOMICS

Co-organised By: ACRP, CRiSP

Supported By: CRC

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Study Site Standard Operating Procedures

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CTC's Generic Study Site SOPS

QA.	**QUALITY ASSURANCE SOPs**
QA1.	Audit
QA2.	Inspection
P.	**PRE STUDY SOPs**
P1.	Pre-Study Visit
P2.	Review of Protocol
P3.	Review of Protocol Amendments
P4.	Review of Investigator's Brochure
P5.	Review of Case Report Form
P6.	Study Organisation and Planning
P7.	Study Team: Definition of Responsibilities
P8.	Recruitment of Subjects
P9.	Pre-Study Planning of Investigational Products
P10.	Pre-Study Planning for Laboratory Investigations
P11.	Investigators' Meeting and Good Clinical Practice Training
P 12.	Institutional Review Board Application and Communications
T.	**TRIAL OPERATION SOPs**
T1.	Site Initiation Visit
T2.	Blinding: Codes and Code Breaking
T3.	Investigational Products Accounting and Dispensing
T4	Case Report Form Completion
T5.	Obtaining Written Informed Consent
T6.	Adverse Event and Serious Adverse Event Reporting
T7.	Monitoring Visit
T8.	Data Clarification
SC.	**Study Closure SOPs**
SC1.	Study Closeout Visit
SC2.	Archiving of Study Data

Staff at the Clinical Trials Centre (CTC) at The University of Hong Kong (HKU) has over the past decade developed a set of generic study site standard operating procedures (SOPs) that can be used at any site conducting sponsored or investigator-initiated human studies.

In addition, each study site is strongly advised to develop their own study site specific SOPs for all procedures and investigations related to the outcome of clinical research studies, e.g. blood pressure, blood sampling, ECG, x-ray, pulmonary function, surgical procedures etc.

According to international recommendations, study site staff should be trained annually on the contents of the SOPs and the educational activities should be documented. We have been using the set of generic SOPs in a 20 hours course module entitled Good Clinical Practice and Study Site Operation with so far over 150 participants.

We plan to publish our generic SOPs in the *Clinical Trial Magnifier* over the next year or so.

You are free to print the SOPs and use them at your site and to modify the contents. The Principle Investigator at the study site is preferably to review and sign the SOPs. Less experienced study site staff can be provided with formal training on the SOPs.

We invite our subscribers to comment on the SOPs. Revised SOPs will subsequently be published in the *Magnifier*.

Over time, the aim is to establish a *Magnifier* standardization group to standardize study site SOPs.

In this *Magnifier* issue we include two Quality Assurance SOPs, which are on the following pages.

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STUDY SITE STANDARD OPERATING PROCEDURE

SOP No: QA1 AUDIT

Version number: _____ **Effective date:** _____

Approved by: _____ _____

Investigator's Name **Signature** / **Date**

Site name: _____

I. Purpose

To describe the procedures relating to the preparation of the study site, prior to the conduct of a site audit by a Sponsor.

II. Other Related Procedures

All SOPs, as Auditors will probably audit against the SOPs in place at the site.

III. Background

An audit is a systematic and independent examination of trial related activities and documents that determines whether a trial or its related activities were conducted, and the data recorded, analysed and accurately reported according to the protocol, Sponsor's SOPs, Good Clinical Practice, and the applicable regulatory requirement(s).

Who will perform the Audit?

In general, a member of the Quality Assurance (QA) department of the Sponsor will undertake an audit. This group has to be independent of the Sponsor's department that is responsible for setting up and managing the clinical trial programme. The head of the QA department often reports directly to the senior management of the Sponsor. In some circumstances, the Sponsor may contract out the audit to an external consultant.

The Audit Timetable

In the first instance, the Auditor will inform the Sponsor's Monitor that an audit is likely to take place. Usually, the Monitor will immediately inform the Investigator, or the Auditor may contact the Investigator directly to inform him/her that an audit is to take place, together with a suggested date and agenda.

Once the audit date has been agreed, the Monitor will contact the Investigator or his/her Clinical Research Coordinator (CRC) to make an appointment for a preaudit visit at the study site. At this meeting, the Monitor will give the Investigator a full briefing regarding what will happen on the day of the audit, and who needs to be present. The Monitor will also undertake a thorough monitoring visit.

Remember, that the Monitor is being assessed also and he/she will want to ensure that the study is going well, the protocol is being followed, the Case Report forms (CRFs) are properly completed and up-to-date, and that the study files are all in order.

IV. Procedures

1. Prior to the Audit

a) The Investigator should notify all those personnel who need to be aware that an audit is to take place. The following provides an example of who might need to be informed:
- Co-Investigator(s)
- CRC
- Study Administrator
- Pharmacy
- Laboratory
- Technical Departments (X-Ray, ECG, etc.)
- Medical Records Personnel

b) Whilst the Monitor will be a great help in preparing the investigational team for an audit, the Investigator should also call a meeting of those involved to ensure that everyone in the team is aware of the following:
- That there is to be an audit
- The purpose of the audit
- When the audit is to take place and who should be present, or be available if required

c) Conduct a thorough review of the following prior to the audit:
- Study Procedures
- Study Protocol
- CRFs
- Source Data
- Study Documentation

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2. Preparation for the Audit

a) Check that suitable facilities are made available for the Auditor. The Auditor will need to have an office or a quiet area in which to work, meet people and examine records. Access to a photocopier may also be a necessary requirement. Ensure that all the requested documentation is available for the Auditor.

b) Ensure that all trial team personnel are available on the day of the audit.

c) Make sure that you have a copy of the most up-to-date Investigator's Brochure (IB) and a signed copy of the final protocol including any protocol amendments.

d) Locate the letter of approval from the Institutional Review Board (IRB) and check that it refers to the final version of the protocol for the study.

e) Identify any protocol amendments and locate the IRB approval letters for these. Record dates of implementation of each protocol amendment and check that the date supersedes the date of approval.

f) Check that there is documentation to confirm that any other information required by the IRB has been supplied e.g. notification of Serious Unexpected Adverse Events.

g) Ensure that the list of study personnel is up-to-date and accurately reflects all personnel who have been involved in the study, no matter how minor their roles. Check that the Curriculum Vitae on file for anyone undertaking assessments, completing CRFs or obtaining informed consent.

h) Make sure that the log of subjects enrolled in the study is up-to-date and complete. If a log of subjects screened is being kept, make sure that this is also current.

i) Inspect all completed informed consent forms and check that these have been signed and dated by the subject and the person taking consent. The date of consent should be prior to any study related procedures. Check that this is the case.

j) Review the eligibility criteria for all subjects who have entered the study. Make detailed notes regarding any subject that does not satisfy the study inclusion criteria.

k) Check that each CRF has been fully completed and that all data are legible.

l) Check the CRFs for inconsistencies regarding medical history, diagnoses, concomitant medications and dates of visits.

m) Make sure that all corrections in the CRF have been signed and dated.

n) For each subject in the study, check the files and records etc. for evidence of Adverse Events (AEs) and ensure that details of all Adverse Events have been recorded in the CRF.

o) Determine whether or not the AEs observed are defined as serious. Refer to the protocol for AE definitions and ensure that all Serious Adverse Events are reported to the Sponsor.

p) Confirm that there is no outstanding documentation relating to any Adverse Events and check that all events have been followed up adequately.

q) If drug accountability is being undertaken by the Investigator, check that all medication packs are accounted for. A high return of unused material in patient supplies is expected.

r) If a pharmacy is dealing with this aspect, visit the pharmacy and ensure that dispensing and return records are available.

s) Ensure that Investigator and each member of the study team are aware that the Auditor will be looking for evidence that each person dealing with the study, particularly the Investigator, can clearly identify the extent of their knowledge and degree of participation throughout the whole study.

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STUDY SITE STANDARD OPERATING PROCEDURE

SOP No: QA2 INSPECTION

Version number: _____ **Effective date:** _____

Approved by: _____ _____

Investigator's Name **Signature** / **Date**

Site name: _____

I. Purpose

The purpose of this SOP is to describe the procedures at the study site prior to, during and after an inspection performed by the regulatory authorities.

II. Other Related Procedures

All SOPs.

III. Background

Inspections performed by regulatory authorities are usually performed for three main reasons; (1) to assure integrity of clinical study data, (2) to assure subject's rights and safety, (3) to permit sound decisions regarding efficacy and safety.

The main objectives of a regulatory inspection are to determine compliance of clinical Investigators with Good Clinical Practice (GCP) guideline(s) and regulations, to assess if monitoring procedures have been satisfactorily implemented by a Sponsor or CRO and to assess whether data submitted to the regulatory authorities from specific studies are substantiated by appropriate records.

IV. Procedures

1. Prior to the Inspection

The first step in preparing for the inspection is to notify all individuals and groups involved with the conduct of the clinical trial.

a) The Sponsor should also be notified and advised that a regulatory inspection is imminent and likely to take place within a time period of for instance two weeks.

b) Contact the Institutional Review Board (IRB) as they may also be contacted during the inspection.

c) Ensure that medical record of all subjects in the study, are available at the time of inspection.

d) Check that there is a signed Informed Consent Form for each patient

e) Organise the Investigator's File according to the following headings:
- Study protocol
- IRB files Initial approval letter
- Amendment approval letter
- Informed Consent documentation
- Correspondence or status reports
- Sponsor correspondence
- Monitoring log
- Laboratory documentation
- Laboratory normal values
- Certification and accreditation certificates
- List of expiry dates for Investigational Product
- Investigational Product accountability

f) Organise the patient's Case Report Forms (CRFs), medical records and all supporting source documents in the same fashion for each patient.

g) Check that each subject enrolled has the following documented information:
- Condition of subject at time of study entry documenting the condition or disease under investigation
- Record of exposure to trial medication
- All concomitant medications and treatments
- Observations and clinical assessments of the subject while on the trial medication
- Laboratory reports
- Diagnostic test results (X-ray's, ECG, etc.)
- Autopsy report, if applicable

h) Ensure that all the members of the study team meet within a day or two of the scheduled inspection.

i) Ensure that adequate facilities such as a quiet working environment are provided for the Inspector to work.

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j) If possible ensure the Inspector has easy access to a photocopier machine without having to ask for it.

2. During the Inspection

a) Ensure that the appropriate study site personnel make themselves available in person, by pager, or telephone to answer any questions during the ongoing inspection.

b) Be prepared to provide a summary of the study team responsibilities refer to Appendix A for an example list.

c) If asked questions by the Inspector, talk and act confidently about your area of responsibility.

d) Provide correct information to the inspection in a timely manner.

e) Seek clarification if you do not fully understand any questions.

f) Do not answer questions if you are not the correct person to give a proper answer.

g) Finally, don't make statements that cannot be supported.

3. After the Inspection

a) The Inspector will, according to their own guidelines inform the necessary persons of the result of the findings.

V. Appendix

Appendix A: Example of a Study Personnel and Responsibilities List

Appendix A: Example of a Study Personnel and Responsibilities List

Title	Name	Responsibilities
Investigator	Doctor Smith, MD Present Position Tel No. Email	Overall supervision of study. Sponsor and IRB communications conduct weekly meetings to discuss study progress.
Co-Investigator	Dr. Tall, MD Present Position Tel No. Email	Subject screening and enrolment. Performs clinical evaluations, document, and report and follow-up adverse events.
CRC	Nurse Green, RN Present Position Tel. No. Email	Explains study procedures to subject/patient; obtains informed consent; schedules follow-up appointments; collects clinical data; performs day to day study procedures.
Technician	Mr./Ms. Quick, BS Present Position Tel No Email	Process and ship blood and urine specimens.
Pharmacist	Mr./Ms. Right, Pharm. D Present Position Tel No. Email	Receive trial medication. Dispensing trial medication to subjects. Maintain trial medication logs. Store returned drugs from subjects/patients. Meets with Monitors.

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Clinical Trial Magnifier – Advisory Board Members

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Clinical Trial Magnifier – Advisory Board Members (cont.)

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Clinical Trial Magnifier – Advisory Board Members (cont.)

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Clinical Trial Magnifier – Advisory Board Members (cont.)

Magnifier Advisory Board – 100 in number

In November/December 2008 we invited our subscribers to become Advisory Board Members of the *Clinical Trial Magnifier*, to be involved in its further development including improvement of content, contributing articles, advising/speaking on an upcoming conference, and participating in a trial management standardization group.

We have now 100 advisors as listed above from 27 countries/regions with about half representing the industry and the other half academia/other sites in Australia, Belgium, Brazil, Canada, China, Denmark, Hong Kong, Hungary, India, Iran, Israel, Italy, Japan, Korea (South), Malaysia, Mexico, Netherlands, Pakistan, Russia, Singapore, South Africa, Spain, Sweden, Taiwan, Turkey, Ukraine, UK and US.

Several of the advisors have contributed with comments to pervious *Magnifier* articles/surveys.

The criteria to become an Advisory Board Member is that you have an interest in clinical trial matters; whether regulatory, ethical, design, medical writing, quality assurance, administration, management or trial conduct. As a member you can contribute as much as you wish and you can leave the Advisory Board at any time.

If you wish to become a *Magnifier* Advisory Board member, please send a message to EditorialBoard@ClinicalTrialMagnifier.com.

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New Trial Registrations (Table 1 of 4)

The most recent industry sponsored clinical trials testing drugs, biologicals or medical devices registered with www.ClinicalTrials.gov; registered from April 1, 2009 and still not activated (Planning) or recruiting (Recruiting) subjects on April 30, 2009.

Status	Link/ID	Type	Phase	Sponsor	Size (n)	Min age	Max age	Condition
Planning	NCT00879216	Drug	1	Vantia	12	65 Yr	N/A	Nocturia
Planning	NCT00879645	Drug	1	Ikaria Holdings	24	18 Yr	65 Yr	Renal Impairment
Planning	NCT00879905	Drug	1	Novartis	65	18 Yr	N/A	Advanced Solid Malignancies
Planning	NCT00883194	Drug	1	Painreform	15	18 Yr	60 Yr	Pain
Planning	NCT00886470	Biological	1	Stemnion	99	18 Yr	40 Yr	Burns
Planning	NCT00888927	Biological	1	Kyowa Hakko Kirin	47	18 Yr	N/A	Peripheral T-Cell Lymphoma
Planning	NCT00878449	Drug	1	Abbott	35	18 Yr	N/A	Small Cell Lung Carcinoma
Planning	NCT00887757	Drug	1	Abbott	25	18 Yr	N/A	Solid Tumor
Planning	NCT00888108	Drug	1	Abbott	25	18 Yr	N/A	Solid Tumor
Planning	NCT00890318	Drug	1	Abbott	32	18 Yr	55 Yr	HCV Infection
Planning	NCT00889837	Drug	1	Alexza	50	40 Yr	65 Yr	Chronic Obstructive Pulmonary Disease
Planning	NCT00890175	Drug	1	Alexza	50	18 Yr	65 Yr	Asthma
Planning	NCT00886756	Drug	1	AstraZeneca	48	20 Yr	45 Yr	Healthy
Planning	NCT00878020	Drug	1	Bristol-Myers Squibb	48	18 Yr	45 Yr	Obesity
Planning	NCT00884546	Drug	1	Bristol-Myers Squibb	66	18 Yr	N/A	Advanced Cancer, Various, NOS
Planning	NCT00886782	Drug	1	Bristol-Myers Squibb	75	18 Yr	N/A	Metastatic Cancer
Planning	NCT00888069	Drug	1	Cytochroma	30	18 Yr	80 Yr	Chronic Renal Failure
Planning	NCT00875979	Drug	1	Genentech	40	18 Yr	N/A	Metastatic Breast Cancer
Planning	NCT00888745	Drug	1	Genentech	65	18 Yr	75 Yr	Rheumatoid Arthritis
Planning	NCT00875446	Drug	1	GlaxoSmithKline	76	18 Yr	80 Yr	Amyotrophic Lateral Sclerosis
Planning	NCT00880321	Drug	1	GlaxoSmithKline	70	18 Yr	N/A	Solid Tumor Cancer
Planning	NCT00884533	Drug	1	GlaxoSmithKline	216	18 Yr	45 Yr	Alzheimer's Disease
Planning	NCT00882674	Drug	1	Hoffmann-La Roche	70	18 Yr	N/A	Breast Cancer
Planning	NCT00887926	Biological	1	Imclone	30	18 Yr	N/A	Myeloid Leukemia
Planning	NCT00884715	Drug	1	Indevus	20	18 Yr	80 Yr	Carcinoid Syndrome
Planning	NCT00890240	Drug	1	Johnson & Johnson	18	6 Yr	11 Yr	Attention Deficit Hyperactivity Disorder
Planning	NCT00890292	Drug	1	Johnson & Johnson	18	12 Yr	17 Yr	Attention Deficit Hyperactivity Disorder
Planning	NCT00873912	Biological	1	Medimmune	300	18 Yr	49 Yr	Healthy
Planning	NCT00874939	Drug	1	Merck	44	65 Yr	N/A	Dementia
Planning	NCT00880568	Drug	1	Merck	92	18 Yr	N/A	Neoplasms, Malignant
Planning	NCT00886613	Biological	1	Merck	120	60 Yr	N/A	Herpes Zoster
Planning	NCT00888238	Drug	1	Merck	12	18 Yr	45 Yr	Type 2 Diabetes Mellitus
Planning	NCT00879866	Biological	1	Merck KGAA	12	18 Yr	N/A	Non Small Cell Lung Cancer
Planning	NCT00876161	Drug	1	Nexbio	29	18 Yr	65 Yr	Healthy
Planning	NCT00878514	Drug	1	Orion	18	18 Yr	55 Yr	Healthy
Planning	NCT00878865	Drug	1	Orion	18	18 Yr	55 Yr	Healthy
Planning	NCT00889382	Drug	1	OSI	169	18 Yr	N/A	Ovarian Cancer
Planning	NCT00875628	Drug	1	Pfizer	24	18 Yr	55 Yr	Healthy Volunteers
Planning	NCT00876304	Drug	1	Pfizer	40	18 Yr	55 Yr	Schizophrenia
Planning	NCT00877539	Drug	1	Pfizer	12	18 Yr	60 Yr	Asthma
Planning	NCT00877955	Drug	1	Pfizer	24	18 Yr	55 Yr	Healthy
Planning	NCT00878189	Drug	1	Pfizer	60	16 Yr	N/A	Solid Tumors
Planning	NCT00879983	Drug	1	Pfizer	24	18 Yr	45 Yr	Healthy
Planning	NCT00886093	Drug	1	Pfizer	10	18 Yr	55 Yr	Healthy
Planning	NCT00880750	Drug	1	Shire	60	18 Yr	55 Yr	End Stage Renal Disease
Planning	NCT00879814	Biological	1	Wyeth	48	18 Yr	40 Yr	Meningitis, Meningococcal
Planning	NCT00878761	Biological	2	Stromedix	48	18 Yr	65 Yr	Chronic Allograft Dysfunction
Planning	NCT00884169	Drug	2	Maruho	Missing	18 Yr	65 Yr	Plaque Psoriasis
Planning	NCT00889967	Drug	2	Aradigm	108	18 Yr	80 Yr	Non-Cystic Fibrosis Bronchiectasis
Planning	NCT00881673	Drug	2	Alcon	120	18 Yr	N/A	Allergic Conjunctivitis
Planning	NCT00874107	Biological	2	Biothera	90	18 Yr	75 Yr	Non-Small Cell Lung Cancer
Planning	NCT00874848	Biological	2	Biothera	90	18 Yr	75 Yr	NSCLC
Planning	NCT00885118	Drug	2	Boehringer Ingelheim	80	20 Yr	70 Yr	Diabetes Mellitus, Type 2
Planning	NCT00874770	Drug	2	Bristol-Myers Squibb	48	18 Yr	70 Yr	Hepatitis C Infection
Planning	NCT00875667	Drug	2	Celgene	150	18 Yr	N/A	Mantle Cell Lymphoma
Planning	NCT00883051	Drug	2	Colucid	450	18 Yr	65 Yr	Migraine Disorders
Planning	NCT00883090	Biological	2	CSL Behring	15	N/A	N/A	Factor Xiii Deficiency
Planning	NCT00888940	Drug	2	Cubist	300	18 Yr	85 Yr	Surgical Procedures, Operative
Planning	NCT00890305	Drug	2	Curetech	168	18 Yr	N/A	Metastatic Colorectal Cancer
Planning	NCT00882999	Drug	2	Eli Lilly	245	18 Yr	64 Yr	Relapsing-Remitting Multiple Sclerosis
Planning	NCT00874796	Drug	2	Gilead	240	18 Yr	65 Yr	HCV Infection
Planning	NCT00878293	Drug	2	Grenenthal	108	18 Yr	75 Yr	Diabetic Polyneuropathy
Planning	NCT00883558	Biological	2	Halozyme	40	18 Yr	65 Yr	Diabetes Mellitus, Type 1
Planning	NCT00884507	Drug	2	Hoffmann-La Roche	420	50 Yr	85 Yr	Alzheimer Disease
Planning	NCT00880217	Drug	2	Johnson & Johnson	426	18 Yr	55 Yr	Attention Deficit Hyperactivity Disorder

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New Trial Registrations (Table 2 of 4)

The most recent industry sponsored clinical trials testing drugs, biologicals or medical devices registered with www.ClinicalTrials.gov; registered from April 1, 2009 and still not activated (Planning) or recruiting (Recruiting) subjects on April 30, 2009.

Status	Link/ID	Type	Phase	Sponsor	Size (n)	Min age	Max age	Condition
Planning	NCT00873860	Drug	2	Medimmune	192	18 Yr	65 Yr	Asthma
Planning	NCT00875056	Drug	2	Merck	54	20 Yr	74 Yr	Lymphoma
Planning	NCT00880763	Drug	2	Merck	120	20 Yr	64 Yr	Hepatitis C
Planning	NCT00879112	Drug	2	Metabasis	80	18 Yr	65 Yr	Hypercholesterolemia
Planning	NCT00887588	Drug	2	Novartis	290	40 Yr	N/A	Chronic Heart Failure
Planning	NCT00876421	Drug	2	Ono	400	18 Yr	80 Yr	Overactive Bladder
Planning	NCT00876187	Biological	2	Pfizer	1,000	18 Yr	N/A	Low Back Pain
Planning	NCT00889889	Biological	2	Solvay	1,250	18 Yr	64 Yr	Influenza
Planning	NCT00882908	Drug	2	Tibotec	400	18 Yr	70 Yr	Hepatitis C
Planning	NCT00880009	Drug	2	Wyeth	250	18 Yr	N/A	Breast Cancer
Planning	NCT00883896	Drug	2	Wyeth	120	18 Yr	N/A	Rheumatoid Arthritis
Planning	NCT00886743	Drug	2	Wyeth	40	18 Yr	65 Yr	Long QT Syndrome
Planning	NCT00876824	Drug	3	Bharat	500	5 Yr	65 Yr	Leishmaniasis, Visceral
Planning	NCT00876850	Drug	3	Paratek	789	18 Yr	N/A	CSSSI
Planning	NCT00877409	Drug	3	Zurita	80	12 Yr	35 Yr	Acne Vulgaris
Planning	NCT00878917	Drug	3	Alfred E. Tiefenbacher	32	18 Yr	N/A	Ocular Hypertension
Planning	NCT00879333	Drug	3	Novartis	633	18 Yr	N/A	Advanced Gastric Cancer
Planning	NCT00881452	Drug	3	Curemark	170	3 Yr	8 Yr	Autism
Planning	NCT00886769	Drug	3	Novartis	122	2 Yr	19 Yr	Systemic Juvenile Idiopathic Arthritis
Planning	NCT00887198	Drug	3	Cougar	1,000	18 Yr	N/A	Prostate Cancer
Planning	NCT00889356	Drug	3	Zodiac	160	18 Yr	50 Yr	Bacterial Vaginosis
Planning	NCT00889863	Drug	3	Novartis	214	2 Yr	19 Yr	Systemic Juvenile Idiopathic Arthritis
Planning	NCT00884585	Drug	3	Allergan	124	12 Yr	N/A	Atopic Conjunctivitis
Planning	NCT00883493	Drug	3	AstraZeneca	412	18 Yr	65 Yr	Acute Bipolar Depression
Planning	NCT00880100	Drug	3	Axcan	50	2 Yr	6 Yr	Pancreatic Insufficiency
Planning	NCT00883116	Drug	3	Bristol-Myers Squibb	370	18 Yr	N/A	Endometrial Cancer
Planning	NCT00885378	Drug	3	Bristol-Myers Squibb	152	18 Yr	78 Yr	Type 2 Diabetes
Planning	NCT00876798	Drug	3	Cardiokine	200	18 Yr	N/A	Euvolemic Hyponatremia
Planning	NCT00876876	Drug	3	Cardiokine	300	18 Yr	N/A	Hypervolemic Hyponatremia
Planning	NCT00885365	Drug	3	Chiesi	320	6 Yr	N/A	Cystic Fibrosis
Planning	NCT00885742	Biological	3	CSL Behring	40	N/A	N/A	Factor Xiii Deficiency
Planning	NCT00884000	Drug	3	Ferring	138	3 Yr	11 Yr	Growth Hormone Deficiency
Planning	NCT00883233	Drug	3	Galderma	120	12 Yr	35 Yr	Acne
Planning	NCT00879229	Drug	3	Gilead	220	40 Yr	80 Yr	Pulmonary Hypertension
Planning	NCT00883779	Drug	3	Hoffmann-La Roche	450	18 Yr	N/A	Non-Small Cell Lung Cancer
Planning	NCT00876395	Drug	3	Novartis	717	18 Yr	N/A	Breast Cancer
Planning	NCT00885079	Drug	3	Otsuka	180	20 Yr	N/A	Dry Eye Syndromes
Planning	NCT00883740	Drug	3	Pfizer	100	18 Yr	64 Yr	Sleep Disorders
Planning	NCT00881842	Biological	3	Solvay	120	18 Yr	N/A	Influenza
Planning	NCT00887978	Drug	3	United	Missing	18 Yr	75 Yr	Pulmonary Hypertension
Planning	NCT00878709	Drug	3	Wyeth	3850	18 Yr	N/A	Breast Cancer
Planning	NCT00887224	Drug	3	Wyeth	850	18 Yr	N/A	Major Depressive Disorder
Planning	NCT00877123	Drug	4	Clalit	80	40 Yr	65 Yr	Obesity
Planning	NCT00883675	Drug	4	Maestro	133	18 Yr	N/A	Non-Small Cell Lung Cancer
Planning	NCT00888381	Biological	4	CSL	120	18 Yr	N/A	Influenza
Planning	NCT00882557	Drug	4	Cubist	12	18 Yr	N/A	Hemodialysis
Planning	NCT00887354	Drug	4	Eli Lilly	242	50 Yr	78 Yr	Osteoporosis
Planning	NCT00884273	Drug	4	Ferring	180	18 Yr	N/A	Prostate Cancer
Planning	NCT00879970	Drug	4	GlaxoSmithKline	16,000	50 Yr	N/A	Type 2 Diabetes Mellitus
Planning	NCT00880438	Biological	4	GlaxoSmithKline	100,000	18 Yr	25 Yr	Cervical Intraepithelial Neoplasia
Planning	NCT00875030	Drug	4	Pfizer	40	18 Yr	55 Yr	Healthy
Planning	NCT00879398	Drug	4	Pfizer	4,500	18 Yr	N/A	Overactive Bladder
Planning	NCT00889603	Drug	4	Pfizer	400	50 Yr	N/A	Vascular Dementia
Planning	NCT00889720	Drug	4	Pfizer	100	18 Yr	N/A	Smoking Cessation
Planning	NCT00878748	Drug	4	Wyeth	700	18 Yr	N/A	Major Depressive Disorder
Planning	NCT00884390	Drug	4	Wyeth	300	12 Yr	N/A	Hemophilia A
Planning	NCT00889668	Device	1	Integrity	158	10 Yr	N/A	Type 2 Diabetes Mellitus
Planning	NCT00888199	Device	2	Tensegrity	80	18 Yr	90 Yr	Amputation
Planning	NCT00889642	Device	2	Dharma	90	18 Yr	N/A	Local Anesthesia
Planning	NCT00887237	Device	3	Medtronic	100	18 Yr	N/A	Heart Failure
Planning	NCT00876278	Device	4	Acri.Tec	30	50 Yr	75 Yr	Cataract
Planning	NCT00883246	Device	4	EV3	800	18 Yr	N/A	Critical Limb Ischemia
Recruiting	NCT00879489	Biological	1	Quantum	24	18 Yr	85 Yr	Breast Cancer
Recruiting	NCT00879749	Biological	1	Nexpep	40	18 Yr	60 Yr	Celiac Disease
Recruiting	NCT00880308	Drug	1	Novartis	58	18 Yr	N/A	Basal Cell Carcinoma

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New Trial Registrations (Table 3 of 4)

The most recent industry sponsored clinical trials testing drugs, biologicals or medical devices registered with www.ClinicalTrials.gov; registered from April 1, 2009 and still not activated (Planning) or recruiting (Recruiting) subjects on April 30, 2009.

Status	Link/ID	Type	Phase	Sponsor	Size (n)	Min age	Max age	Condition
Recruiting	NCT00883727	Drug	1	Stempeutics	20	20 Yr	70 Yr	Myocardial Infarction
Recruiting	NCT00883870	Drug	1	Stempeutics	20	18 Yr	60 Yr	Critical Limb Ischemia
Recruiting	NCT00886353	Biological	1	Apeiron	22	18 Yr	N/A	Cancer Diseases
Recruiting	NCT00886496	Biological	1	Enzon	48	2 Yr	17 Yr	Unspecified Childhood Solid Tumor
Recruiting	NCT00886808	Drug	1	ICO	15	18 Yr	N/A	Diffuse Diabetic Macular Edema
Recruiting	NCT00888693	Drug	1	Abbott	35	18 Yr	55 Yr	Schizophrenia
Recruiting	NCT00882869	Drug	1	Aegera	75	18 Yr	N/A	Advanced Hepatocellular Carcinoma
Recruiting	NCT00873769	Drug	1	Alexza	36	20 Yr	50 Yr	Smoking, Cigarette
Recruiting	NCT00874237	Drug	1	Alexza	48	18 Yr	65 Yr	Healthy
Recruiting	NCT00882180	Drug	1	Alnylam	58	18 Yr	N/A	Solid Tumors
Recruiting	NCT00875160	Drug	1	Amicus	8	18 Yr	65 Yr	Type 1 Gaucher Disease
Recruiting	NCT00874042	Drug	1	Arqule	32	18 Yr	N/A	Advanced Solid Tumors
Recruiting	NCT00887627	Drug	1	Astellas	24	18 Yr	70 Yr	Hyponatremia
Recruiting	NCT00878423	Drug	1	Astex	40	18 Yr	N/A	Metastatic Solid Tumors
Recruiting	NCT00879346	Drug	1	AstraZeneca	24	18 Yr	55 Yr	Healthy
Recruiting	NCT00886067	Drug	1	AstraZeneca	12	20 Yr	45 Yr	Healthy
Recruiting	NCT00886366	Drug	1	AstraZeneca	26	20 Yr	40 Yr	Type 2 Diabetes
Recruiting	NCT00887770	Drug	1	AstraZeneca	64	18 Yr	45 Yr	Rheumatoid Arthritis
Recruiting	NCT00885937	Drug	1	Bayer	33	18 Yr	N/A	Healthy
Recruiting	NCT00884949	Drug	1	Biomarin	20	5 Yr	18 Yr	MPS IV A
Recruiting	NCT00882726	Drug	1	Centocor	116	18 Yr	65 Yr	Diabetes Mellitus, Type 2
Recruiting	NCT00875264	Drug	1	Cephalon	30	18 Yr	N/A	Cancer
Recruiting	NCT00883935	Drug	1	GlaxoSmithKline	24	18 Yr	65 Yr	Healthy
Recruiting	NCT00878111	Drug	1	Molmed	16	18 Yr	N/A	Solid Tumours
Recruiting	NCT00877032	Biological	1	Pfizer	45	18 Yr	N/A	Macular Degeneration
Recruiting	NCT00879684	Biological	1	Pfizer	45	18 Yr	N/A	Malignancy
Recruiting	NCT00886821	Biological	1	Pfizer	48	18 Yr	70 Yr	Diabetes Mellitus, Type 2
Recruiting	NCT00877474	Drug	1	Pharmamar	35	18 Yr	N/A	Advanced Solid Tumors
Recruiting	NCT00884845	Drug	1	Pharmamar	35	18 Yr	N/A	Advanced Malignant Solid Tumors
Recruiting	NCT00875316	Drug	1	Phytopharm	36	40 Yr	80 Yr	Parkinson's Disease
Recruiting	NCT00882063	Drug	1	Piramal	32	18 Yr	80 Yr	Multiple Myeloma
Recruiting	NCT00881062	Drug	1	Repros	6	18 Yr	50 Yr	Excretion
Recruiting	NCT00881608	Drug	1	Repros	10	18 Yr	45 Yr	Amenorrhea
Recruiting	NCT00876044	Drug	1	Sanofi-Aventis	80	18 Yr	N/A	Cancer
Recruiting	NCT00879099	Drug	1	Santen	12	18 Yr	40 Yr	Healthy
Recruiting	NCT00881166	Drug	1	Supergen	105	18 Yr	N/A	Malignant Disease
Recruiting	NCT00878722	Drug	1	Topotarget	35	18 Yr	N/A	Acute Myeloid Leukemia
Recruiting	NCT00878800	Drug	1	Topotarget	65	18 Yr	N/A	Soft Tissue Sarcomas
Recruiting	NCT00877799	Drug	2	Cara	120	21 Yr	60 Yr	Post-Operative Pain
Recruiting	NCT00878072	Drug	2	Novartis	50	12 Yr	18 Yr	Herpes Labialis
Recruiting	NCT00879658	Drug	2	Novartis	275	18 Yr	55 Yr	Multiple Sclerosis
Recruiting	NCT00881075	Drug	2	Eagle	30	18 Yr	N/A	Myocardial Infarction
Recruiting	NCT00881140	Drug	2	Biopro	30	30 Yr	53 Yr	Vaginal Bleeding.
Recruiting	NCT00882024	Drug	2	Nuon	250	18 Yr	75 Yr	Active Rheumatoid Arthritis
Recruiting	NCT00885196	Drug	2	Novartis	336	18 Yr	75 Yr	Plaque Psoriasis
Recruiting	NCT00889473	Drug	2	Alba	80	18 Yr	72 Yr	Celiac Disease
Recruiting	NCT00879606	Drug	2	Altor	120	18 Yr	N/A	Acute Respiratory Distress Syndrome
Recruiting	NCT00878501	Drug	2	AstraZeneca	520	40 Yr	80 Yr	Pain
Recruiting	NCT00875433	Drug	2	Boehringer Ingelheim	60	18 Yr	N/A	Neoplasms
Recruiting	NCT00881530	Drug	2	Boehringer Ingelheim	688	18 Yr	N/A	Diabetes Mellitus, Type 2
Recruiting	NCT00888719	Drug	2	Choongwae	120	25 Yr	75 Yr	Type 2 Diabetes Mellitus
Recruiting	NCT00878774	Biological	2	Circassia	50	18 Yr	65 Yr	Allergy
Recruiting	NCT00879541	Biological	2	CSL Behring	62	12 Yr	N/A	Hemophilia A
Recruiting	NCT00879086	Drug	2	Eisai	98	18 Yr	N/A	Breast Cancer
Recruiting	NCT00887549	Drug	2	Eli Lilly	60	18 Yr	N/A	Non-Small Cell Lung Cancer
Recruiting	NCT00880399	Drug	2	GlaxoSmithKline	350	18 Yr	64 Yr	Depression
Recruiting	NCT00887341	Drug	2	Hoffmann-La Roche	80	18 Yr	N/A	Rheumatoid Arthritis
Recruiting	NCT00876252	Biological	2	Intercell	450	18 Yr	80 Yr	Ventilated Associated Pneunomia
Recruiting	NCT00875277	Drug	2	Leo	24	18 Yr	N/A	Psoriasis Vulgaris
Recruiting	NCT00879242	Drug	2	Novartis	50	10 Yr	N/A	Beta Thalassemia Transfusion
Recruiting	NCT00887861	Drug	2	Novartis	45	18 Yr	65 Yr	Epilepsy
Recruiting	NCT00888004	Drug	2	Novartis	34	30 Yr	85 Yr	L-Dopa Induced Dyskinesia
Recruiting	NCT00877903	Drug	2	Osiris	220	21 Yr	85 Yr	Myocardial Infarction
Recruiting	NCT00884286	Drug	2	PharmaMar	58	18 Yr	N/A	Lymphoma

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Status	Link/ID	Type	Phase	Sponsor	Size (n)	Min age	Max age	Condition
Recruiting	NCT00884312	Drug	2	Proteolix	100	18 Yr	N/A	Multiple Myeloma
Recruiting	NCT00889707	Drug	2	Protox	81	40 Yr	80 Yr	Benign Prostatic Hyperplasia
Recruiting	NCT00875524	Biological	2	Sanofi-Aventis	180	2 Yr	45 Yr	Dengue Disease
Recruiting	NCT00880893	Biological	2	Sanofi-Aventis	1,200	2 Yr	45 Yr	Dengue Diseases
Recruiting	NCT00884182	Biological	2	Sanofi-Aventis	350	6 Mth	17 Yr	Orthomyxovirus Infections
Recruiting	NCT00885157	Biological	2	Sanofi-Aventis	228	15 Mth	18 Mth	Poliomyelitis
Recruiting	NCT00889486	Drug	2	Tranzyme	80	18 Yr	80 Yr	Diabetes Mellitus
Recruiting	NCT00876538	Drug	2	Trophos	40	18 Yr	80 Yr	Chemotherapy-Induced Peripheral Neuropathy
Recruiting	NCT00882414	Drug	2	Vifor	80	18 Yr	60 Yr	Iron Deficiency
Recruiting	NCT00876486	Drug	3	Samyang	Missing	18 Yr	N/A	Breast Cancer
Recruiting	NCT00876694	Drug	3	Novartis	180	40 Yr	N/A	Chronic Obstructive Pulmonary Disease
Recruiting	NCT00877383	Drug	3	Novartis	1126	40 Yr	N/A	Chronic Obstructive Pulmonary Disease
Recruiting	NCT00890097	Drug	3	Alcon	550	55 Yr	N/A	Age Related Macular Degeneration
Recruiting	NCT00876447	Biological	3	Allergan	500	18 Yr	N/A	Overactive Bladder
Recruiting	NCT00877890	Drug	3	Amylin	244	18 Yr	N/A	Type 2 Diabetes Mellitus
Recruiting	NCT00882518	Drug	3	AstraZeneca	250	18 Yr	65 Yr	Schizophrenia
Recruiting	NCT00888082	Drug	3	AstraZeneca	102	18 Yr	45 Yr	Ovarian Function
Recruiting	NCT00884260	Drug	3	Bayer	915	18 Yr	40 Yr	Contraception
Recruiting	NCT00877006	Drug	3	Cephalon	296	18 Yr	N/A	Mantle Cell Lymphoma
Recruiting	NCT00883753	Drug	3	Hoffmann-La Roche	1,000	18 Yr	N/A	Rheumatoid Arthritis
Recruiting	NCT00887822	Drug	3	Hoffmann-La Roche	200	18 Yr	N/A	Gastric Cancer
Recruiting	NCT00880620	Drug	3	Impax	350	30 Yr	N/A	Parkinson's Disease
Recruiting	NCT00882375	Drug	3	Johnson & Johnson	465	18 Yr	N/A	Smoking Cessation
Recruiting	NCT00883168	Drug	3	Meda	1,800	12 Yr	N/A	Seasonal Allergic Rhinitis
Recruiting	NCT00885170	Drug	3	Merck	160	60 Yr	N/A	Osteoporosis
Recruiting	NCT00885352	Drug	3	Merck	266	18 Yr	78 Yr	Type 2 Diabetes Mellitus
Recruiting	NCT00876343	Drug	3	Otsuka	540	20 Yr	74 Yr	Major Depressive Disorder
Recruiting	NCT00882362	Drug	3	Otsuka	100	20 Yr	N/A	Major Depressive Disorder
Recruiting	NCT00883337	Drug	3	Sanofi-Aventis	300	18 Yr	N/A	Multiple Sclerosis
Recruiting	NCT00889330	Drug	3	Vistakon	60	10 Yr	N/A	Allergic Conjunctivitis
Recruiting	NCT00877149	Drug	4	Novartis	80	16 Yr	N/A	Compensated Chronic Hepatitis B
Recruiting	NCT00878670	Drug	4	Max Zeller Soehne	30	2 Yr	45 Yr	Neurodermatitis
Recruiting	NCT00881205	Drug	4	Novartis	200	18 Yr	55 Yr	Cognitive Impairment
Recruiting	NCT00874887	Drug	4	Allergan	66	50 Yr	N/A	Anti-Biotic Resistance
Recruiting	NCT00874679	Drug	4	Bayer	5,000	18 Yr	N/A	Erectile Dysfunction
Recruiting	NCT00874926	Drug	4	Bayer	150	N/A	N/A	Haemophilia A
Recruiting	NCT00889226	Drug	4	Choongwae	200	25 Yr	75 Yr	Hypercholesterolemia and Diabetes
Recruiting	NCT00878878	Drug	4	Ge Healthcare	30	18 Yr	N/A	Pulmonary Hypertension
Recruiting	NCT00881868	Drug	4	Galderma	80	18 Yr	N/A	Scalp Psoriasis
Recruiting	NCT00877357	Biological	4	Shantha	3,000	6 Weeks	8 Weeks	Haemophilus Influenzae Type B
Recruiting	NCT00887484	Drug	4	Stiefel	45	21 Yr	N/A	Acne Vulgaris
Recruiting	NCT00878527	Device	1	Circulite	30	18 Yr	75 Yr	Heart Failure
Recruiting	NCT00884962	Device	1	Aeris	Missing	40 Yr	N/A	Advanced Emphysema
Recruiting	NCT00874835	Device	2	Ocular Systems	100	45 Yr	N/A	Corneal Transplantation
Recruiting	NCT00878579	Device	2	Interventional Spine	292	18 Yr	70 Yr	Lumbar Degenerative Disc Disease
Recruiting	NCT00886899	Device	2	Bridgepoint	149	18 Yr	N/A	Coronary Artery Chronic Total Occlusion
Recruiting	NCT00881257	Device	2	Minnow	50	18 Yr	N/A	Peripheral Vascular Disease
Recruiting	NCT00881023	Device	3	ATRM	300	18 Yr	65 Yr	Osteochondritis Dissecans
Recruiting	NCT00882219	Device	3	Abbott	100	18 Yr	N/A	Coronary Restenosis
Recruiting	NCT00889252	Device	3	Vistakon	250	8 Yr	N/A	Allergic Conjunctivitis
Recruiting	NCT00886119	Device	4	Novartis	40	35 Yr	N/A	Presbyopia

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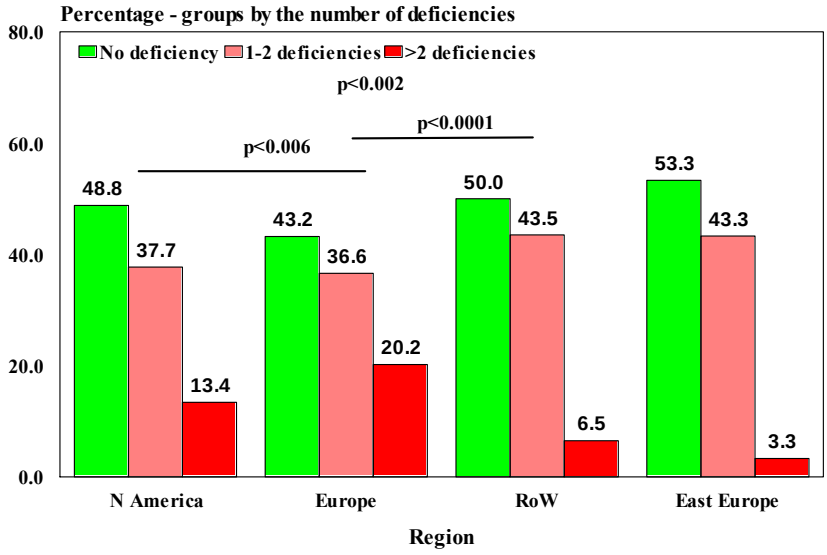

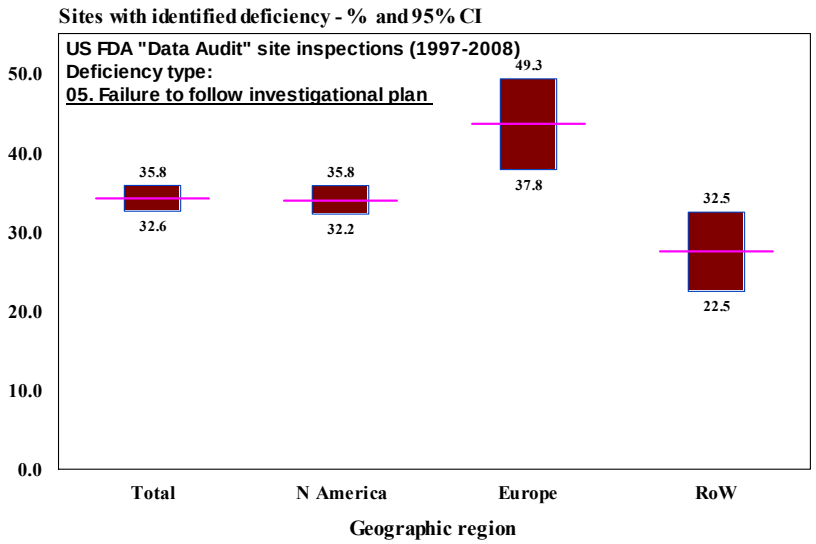

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