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RESEARCH ARTICLE

FDA Clinical Investigator Inspection List, who is Inspected and What are the Results for Countries Outside US?

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ABSTRACT

Background: The purpose of this analysis was to revisit the open US Food and Drug Administration (FDA) inspection list results from clinical trials and show the possibilities of evaluating inspection results between different world regions and explore what aspects of clinical trial deficiencies are most often reported.

Aims: The aim of this study was to evaluate inspection results from different regions of the world and the deficiencies most often reported.

Methods: On October 10, 2021, the clinical Investigator Inspection List was download as an Excel spreadsheet (Microsoft, Seattle, USA) from the FDA homepage. Data were extracted and categorized as: Number of inspections in each region and country, number and % of actions found during the inspections, number and % of deficiencies found – in total and in the different regions and countries. No statistical comparison was made on the analysed data in the article.

Results: The total number of inspections performed by the FDA outside the US between 1980 and October 2021 was 3,222. The number of voluntary actions varies in the same manner as the number of inspections. The number of "no actions indicated" increased after 1994, which may indicate that adding new and smaller countries to participate in clinical trials does not affect the quality of the clinical trials. The results shows that most common action registered by the FDA was "voluntary actions indicated (VAI)" (56.6%) followed by "no action indicated (NAI)" (38.6%), while "official action indicated (OAI)" were rare (4.1%). "VAI" and "NAI" were registered in all regions. "VAI" were indicated for topics related to documentation and reporting in 787 inspections (24.4%), protocol violation in 683 inspections (21.2%)), informed consent/institutional review board in 257 inspections (8.0%). The same type of deficiencies was noted for "OAI"; however, these were significantly rarer.

Conclusion: The US Food and Drug Administration only monitors a small number of all clinical trials performed worldwide (1.3%). Despite the large difference in the number of FDA inspections performed in different regions worldwide, the structure of inspection findings is remarkably similar across the globe.

Introduction

The development of clinical medicine requires a continuous search for new drugs and new medical devices, as well as new target areas and new indications for existing drugs. There are currently well-accepted international guidelines in place for clinical trial execution.[1] Clinical trials aim to show that new drugs, devices, and treatments are both safe and effective. When a new treatment regimen is to be approved, high demands are placed on competent review systems. This task is handled by pharmaceutical and medical technology companies, clinical research organisations (CROs) as well as drug control authorities in individual countries. The drug control authorities inspect research sites to verify that clinical trials are conducted in accordance with accepted ethical research principles within the regulatory framework of Good Clinical Practice (GCP).[2]

In May 2021, new regulations for evaluation of the clinical safety and efficacy of medical devices were introduced by the European Union. This will likely result in more clinical trials in this field.[3] In recent decades, clinical trials have expanded beyond traditional national borders as the scientific concept required larger groups of trial participants. Also, it is not economically feasible to conduct a clinical trial within a single country. As new trials require large numbers of participating sites and large numbers of trial participants,[4] internationally uniform rules for collecting and reviewing data were adopted. Another consequence of globalisation of clinical research is that data collected in one country forms the basis for assessment when registering in another country. Rules for data collection and quality review are defined in the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[1]. Starting in 2000, all ongoing clinical studies must be registered on clinicaltrials.gov. In the clinicaltrials.gov database, there are 420,607 studies listed for 221 countries. Of these, 219,364 studies (52%) are conducted outside the US, 133,332 studies (33%) are conducted in US, and 20,908 studies (5%) are conducted in both the US and in non-US countries, while for 47,003 studies (11%), countries are not indicated.[4] EudraCT database is another source of information regarding clinical trials; it was launched on May 1, 2004 and currently lists 42,357 studies from regions around the globe.[5]

Pharmaceutical and medical technology companies perform their own quality reviews of clinical trials and individual research centers, most often with the help of CROs, but these results are usually not disclosed. The regulatory authorities may require more transparency regarding quality indicators for clinical trials. However, regulatory authorities in Sweden[6] and the EU[7] do not publish results of their clinical trial inspections. By contrast, the US Food and Drug Administration (FDA) does publish inspection results.[8] The FDA publishes a list of its inspections via the Clinical Investigator Inspection List on its website.[9] This register lists inspections performed from 1977 to date in 77 countries around the world.

The registry enables independent review of clinical trial inspection results at many research centers and clinical institutions. The registry reports data on responsible researchers, research centers, location of institution, the inspector, and detailed information about findings of the audit. The FDA conducted its first inspections outside the United States in 1980 - in Argentina, Mexico and New Zealand. The first European country inspected for an international trial was the United Kingdom in 1981. Subsequently, pharmaceutical, and medical technology companies expanded their operations to other parts of the world: Asia (Malaysia 1984), Middle East (Israel 1992), Africa (South Africa 1994) and Eastern Europe (Ukraine 1996), for each country's first inspection date, see Appendix 1.[10] To be accepted by the FDA for clinical trials, one must adapt to the FDA's regulatory framework. While the FDA has no jurisdiction to sanction any errors in clinical trials outside the United States, it has the right to exclude all data from the responsible investigator if incorrect data has been found. The Clinical Investigator Inspection List has been evaluated previously with focus on Eastern Europe's participation in clinical trials,[11-13] and one former analysis has been previously performed regarding the frequency of compliance problems, with the rationale that studies have ever more complex protocols.[14] However, this analysis was performed over 10 years ago. Therefore, the purpose of our analysis was to revisit the FDA inspection list results from clinical trials and to show the possibilities for comparing inspection results between different world regions outside US and explore what aspects of a clinical trial deficiencies are most often reported.

Methods

This prospective observational study evaluated the clinical investigator inspection list that contains detailed information about FDA inspections findings of investigational new drug studies performed in US and around the world. The focus of this study was to evaluate results of FDA inspections outside the US. The clinical investigator inspection list is updated quarterly. Inspections are classified according to a

five-point scale with sub-categories with the overall inspection result. This is reported and made as a publicly accessible list of names, addresses, and other relevant information gathered from inspections of clinical investigators from countries that have performed and are performing studies.

The three main categories that report on inspection findings are:

- 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 discover do not warrant further regulatory action. Any corrective action is left up to the investigator to take voluntarily.
- OAI - Official Action Indicated. Objectionable conditions were found, and regulatory and/or administrative sanctions by the FDA are indicated (Figure 1 A).

Other codes are also reported as: "cancelled before start of inspection" (CANC) and "washout" – no meaningful information obtained (WASH); however, these do not include any detailed information regarding deficiency codes, and therefore were not the focus of our evaluation.

Each investigator is identified by a unique investigator ID number. For each inspection, the start date and classification code indicating the focus of the inspection is noted. The FDA inspection list also contains a detailed description of remarks made during the inspection, with the remarks coded on a 23-category scale (Figure 1 B). These 23 codes enable one to thoroughly evaluate the remarks made during the inspection. As an overview of the most difficult tasks in clinical trials, we grouped the deficiency codes into four categories:

1. Investigational study protocol-related (codes 05, 07, 13)
2. Documentation and accountability issues (codes 01, 04, 06, 10, 12, 16)
3. Ethical issues such as institutional review board topics or informed consent issues (codes 02, 03, 08, 14, 15, 17, 20)
4. Others.

Figure 1. *shows (A.) the Clinical Investigator Inspection List Database Codes and Classifications and (B.) the Clinical Investigator Inspection List Deficiency Codes (Reproduced from: https://www.fda.gov/drugs/enforcement-activities-fda/clinical-investigator-inspection-list-ciil-database-codes).*

A.

Codes	Classification
No Action Indicated (NAI)	No objectionable conditions or practices were found during the inspection.
Voluntary Action Indicated (VAI)	Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.
VAI2	No response requested
VAI2C	Consent problems found
VAI3	Response requested
VAI3C	Case closed
VAI3F	Follow-up for cause inspection issued
VAI3R	Response received and accepted
VAIRC	30-day response requested, and case closed
VAIRR	30-day response requested received, and accepted
VAIR	30-day response requested
Official Action Indicated (OAI)	Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.
OAIC	Completed
OAIR	Response requested
OAIRR	Response requested and accepted
OAIW	Voluntary Action Indicated
Cancelled (CANC)	The inspection assignment was canceled before the inspection was started.
Washout (WASH)	An inspection was initiated but no meaningful information could be obtained.

B.

Deficiency Code	Deficiencies
00	No deficiencies noted
01	Records availability
02	Failure to obtain and/or document subject consent
03	Inadequate informed consent form
04	Inadequate drug accountability
05	Failure to follow investigational plan
06	Inadequate and inaccurate records
07	Unapproved concomitant therapy
08	Inappropriate payment to volunteers
09	Unapproved use of drugs before investigational drug submission
10	Inappropriate delegation of authority
11	Inappropriate use/commercialization of investigational drug
12	Failure to list additional investigators
13	Subjects receiving simultaneous investigational drugs
14	Failure to obtain or document IRB approval
15	Failure to notify IRB of changes, failure to submit progress reports
16	Failure to report adverse drug reactions
17	Submission of false information
18	Other not specified
19	Failure to supervise or personally conduct the clinical investigation
20	Failure to protect the rights, safety, and welfare of subjects
21	Failure to permit FDA access to records
NG	Not Given

On October 10, 2021, the clinical Investigator Inspection List was downloaded as an Excel spreadsheet (Microsoft, Seattle, USA) from the FDA homepage. Data were extracted and categorized as:

- Number of inspections in each region and countries outside the US
- Number and % of actions found in total during inspections outside the US
- Number and % of actions found in the different regions outside the US
- Number and % of actions found in the different countries outside the US
- Number and % of deficiencies found in total outside the US
- Number and % of deficiencies in the different regions outside the US
- Number and % of deficiencies in the different countries outside the US.

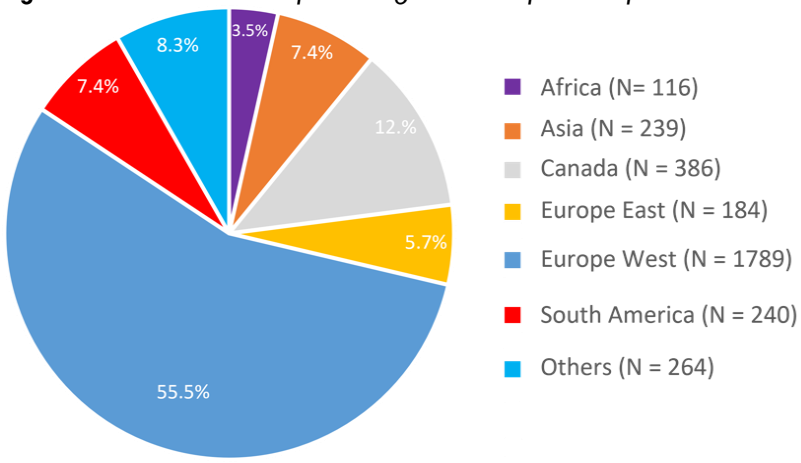
This analysis was done to explore whether there were differences between regions and countries outside the US in regards of findings relating to specific actions performed during a clinical trial.

However, no statistical comparison was made of analysed data due to vast differences in the number of inspections performed in different regions and countries, which would not make statistical comparison meaningful.

Results

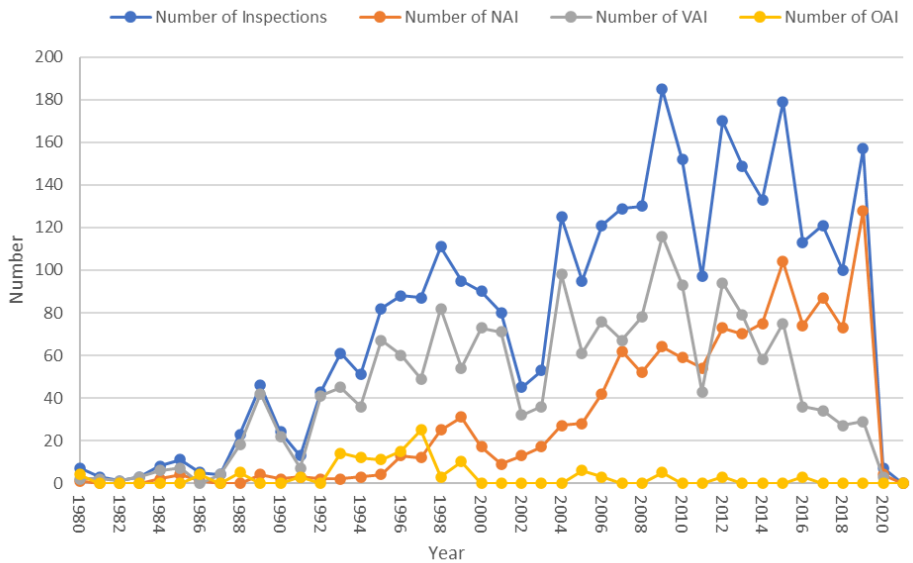
A total of 3,222 inspections were performed by the FDA outside the US between 1980 and October 2021. Most inspections were performed in Europe West (55.5%) followed by Canada (12.0%), Others (8.3%), South America and Asia (7.4%), Europe East (5.7%) and Africa (3.5%) (Figure 2.). However, the number of participating countries in the different regions varies greatly. When analysing individual countries' contribution to each region, most inspections were performed in South Africa (80.4% of Africa region), China (30.1% of Asia region), Russia (70.1% of Europe East region), United Kingdom (13.5% of Europe West region), Argentina (38.8% of South America region) and India (31.8 % of the remaining countries, "Others" in Figure 2). For the total number of inspections in all countries, see Appendix 2.

Figure 2. *The number and percentage of all inspections performed for the different regions are shown.*



The number of inspections grew between 1980 and 1998, then dropped between 1999 and 2003, and then grew again. The number of "OAI" was highest between 1993 and 1999, and there were very few thereafter. The number of "VAI" varies with the number of inspections. The number of "NAI" findings grew after 1994, which may indicate that adding new and smaller countries to in clinical trials does not affect clinical trial quality (Figure 3.).

Figure 3. *Shows the number of inspections between 1980 and 2020 and their correlation to the three deficiency codes.*



The above graphic (with numerical values presented in Table 1) shows that the most common finding codes registered by the FDA was "VAI", followed by "NAI", and "OAI". Figure 3 demonstrates that the overall number of "VAI" findings per year demonstrated a stable downslope trend over the last ten years while the number of inspections "NAI" codes successively increased during the same period. "No Action Indicated" and "VAI" findings were registered in all regions. The "VAI" was indicated for issues related to documentation and reporting in 787 inspections (24.4%), protocol violations in 683 inspections (21.2%), and informed consent/institutional review board in 257 inspections (8.0%). "Official actions indicated" were indicated for documentation and reporting issues (61 inspections, 1.9%), protocol violations (31 inspections, 0.9%), informed consent/institutional review board related issues (20 inspections, 0.6%) (Table 1 and Figure 3).

Table 1. *Inspection results regarding classification and deficiencies for inspections performed by the FDA outside the US between January 1980 and October 2021. Findings were grouped as Findings relating to Protocol Violation, Findings relating to Documentation and Reporting, Findings relating to Informed Consent/Institutional Review Board (IRB) and Other unspecified findings; for detailed information regarding specific deficiency codes see Appendix 4.*

Classification and deficiency codes (N 3222)	**N (%) of the total number of inspections**
No Action Indicated: No objectionable conditions or practices were found during the inspection (N (%) of the total number of inspections).	1,243 (38.6%)
Voluntary Action Indicated (VAI): Objectionable conditions were found, but the problems do not justify further regulatory action. Any corrective action is left up to the investigator to take voluntarily (N (%) of the total number of inspections).	1,824 (56.6%)
Findings relating to the deficiency Code VAI	
Findings relating to Documentation and Reporting	787 (24.4%)
Findings relating to Protocol Violation	683 (21.2%)
Findings relating to Informed Consent/IRB	257 (8.0%)
Other unspecified findings	97 (3.0%)
Official Action Indicated (OAI): Objectionable conditions were found, and regulatory and/or administrative sanctions by FDA are indicated (N (%) of the total number of inspections).	126 (3.9%)
Findings relating to the deficiency code OAI	
Findings relating to Documentation and Reporting	61 (1.9%)
Findings relating to Protocol Violation	31 (1.0%)
Findings relating to Informed Consent/IRB	20 (0.6%)
Other unspecified findings	14 (0.4%)

Figure 3. *Distribution of specific type of findings in inspections that resulted in either Voluntary Action Indicated (VAI) and Official Action Indicated (OAI) codes.*

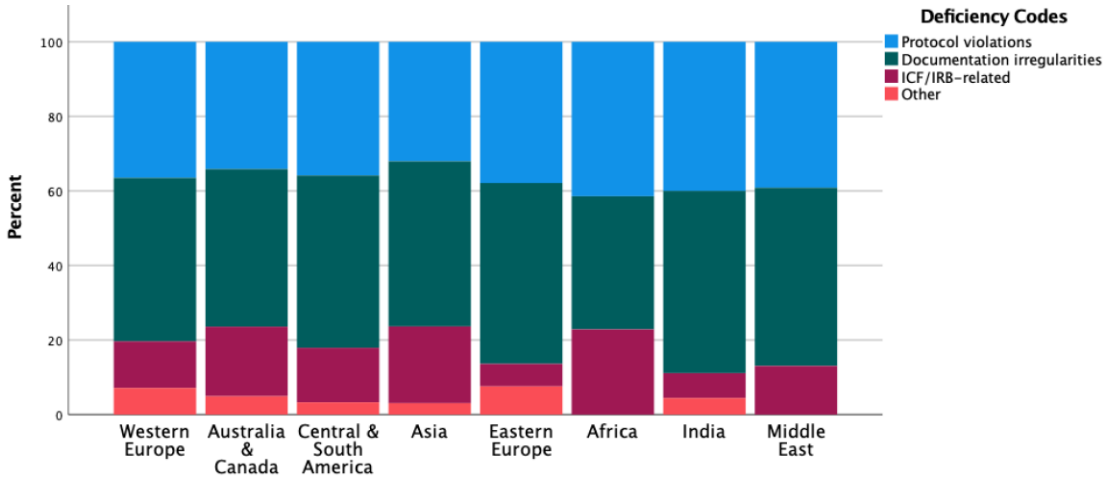
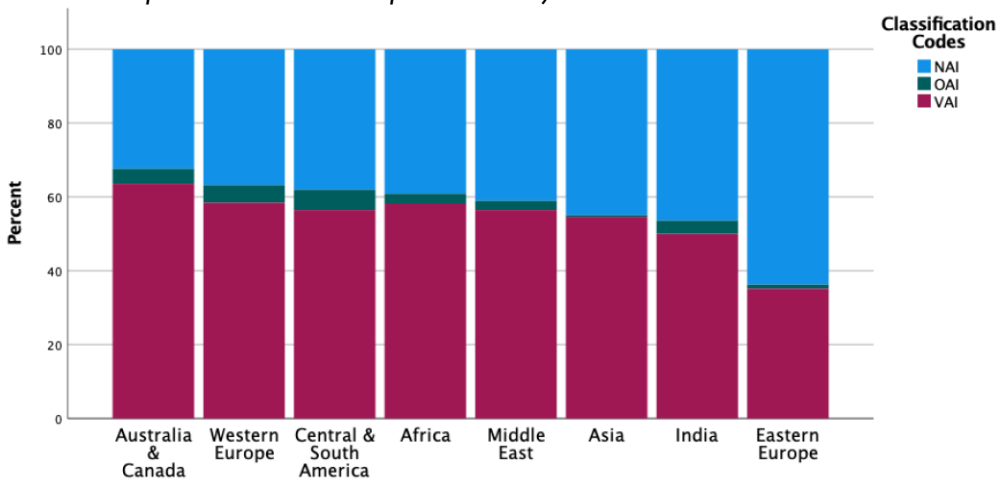


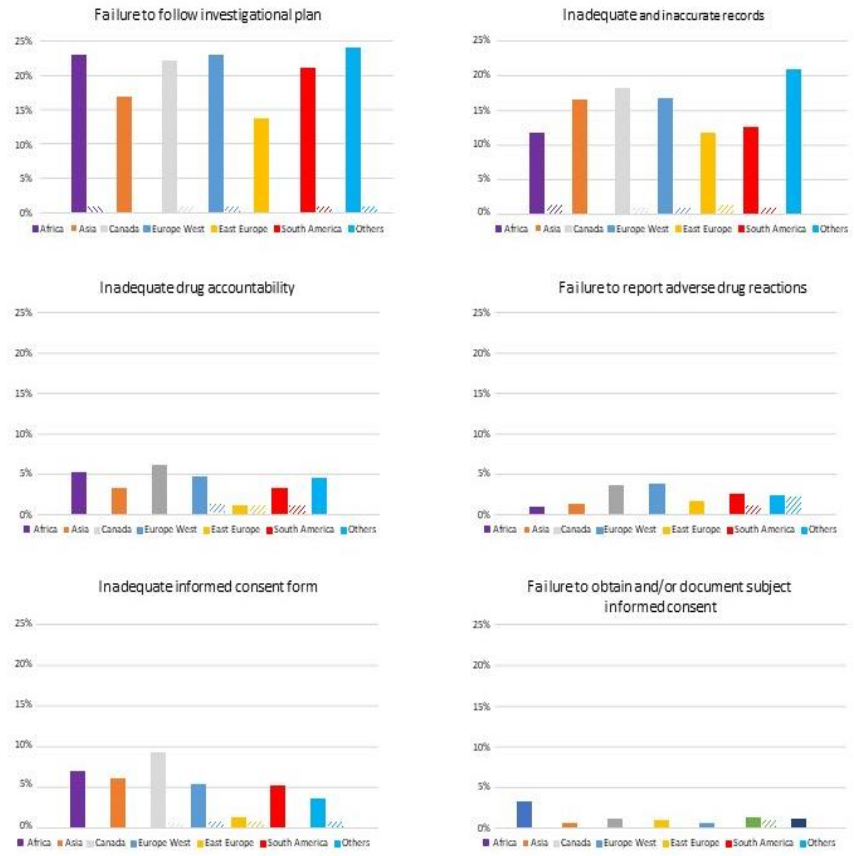
Figure 4 shows the distribution of "NAI", "VAI" and "OAI" findings during FDA inspections outside the US. Notably, the number of inspections resulting in an "NAI" code was remarkably similar across different regions – around 40-50% - except for Eastern Europe, where as many as 64% of all FDA inspection findings were coded as "NAI".

Figure 4. *Distribution of FDA inspection findings coded as "No Action Indicated" (NAI), "Voluntary Action Indicated" (VAI) and "Official Action Indicated" (OAI) across different non-US regions (in the order of prevalence of NAI inspection codes).*



For comparison of most common categories of deficiencies in different regions, see Figure 5. For a detailed description of the 3,222 findings of all classification and deficiency codes for different regions, see Appendix 3.

Figure 5. *Comparison of the six most common deficiencies noted by the FDA in the different regions. Data is presented as percentages of the total number of inspections in each region. Solid columns show the percentage of "Voluntary Action indicated (VAI)", while dashed columns show "Official Action indicated (OAI)".*



Voluntary action indicated findings was noted by the FDA in all regions; but just 21 of the 77 countries had "OAI" findings (the most severe deficiency code) reported, though their absolute number was low (the absolute numbers of "OAI" findings per region and country are given between brackets below):

Africa: South Africa (1) Nigeria (2).
Asia: China (1).
Canada: (13).
Europe West: United Kingdom (21), Belgium (12), Italy (11), Germany (11), France (6), Netherlands (6), Spain (6), Sweden (5), Finland (4), Croatia (3) Turkey (1).
Europe East: Russia (2).
South America: Mexico (8), Peru (7), Argentina (4) and
Others: New Zealand (4), India (3).

Most countries inspected did not have "OAI" findings reported (n=56). One could anticipate that "OAI's" findings might be similar despite this. But it seems that the number of "OAI" findings increases with the number of inspections as most of the countries with "OAI" findings were countries with high numbers of inspections.

Discussion

The US Food and Drug Administration performed 3,222 inspections outside the US between 1980 and October 2021. This represents just 7.6% of the clinical trials registered at the EudraCT databases.[6] It would be interesting to have more data as it would be interesting to see if there were more reviews available of high quality from clinical trials and individual research centers. Also, results from regulatory authorities from EU[8] and individual member states like Sweden[7] could have contributed to more knowledge in this field from the individual countries (but as we noted above, these agencies do not publish their inspections findings). While

more data are available from the US clinical inspections list[9], our focus was to evaluate inspection results between different world regions outside the US.

In an analysis of the clinical investigation list that included data from the US published ten years ago, the authors found differences between Europe East, Europe West, and US regions in regards of deficiencies as failure to follow the investigational plan, inadequate informed consent form and inadequate and inaccurate records. They also noted that the most common deficiencies were related to investigational study protocol, documentation, accountability and ethical issues, institutional review board or informed consent issues in the US and Europe East, Europe West[13]. Thus, although these differences in findings the topic seems to be the same as found in this evaluation. Thus, despite well-accepted international guidelines for clinical trial execution[1], similar deficiencies still occur in clinical trials around the world.

We found that most FDA-identified deficiencies did not justify further regulatory action i.e., NAI findings. When adding the results of inspections to the findings that were objectionable regarding documentation or practices, most trials seemed to be conducted in accordance with international clinical trial guidelines.[1] Official actions indicated findings were few despite the fact that clinical trials are expanding geographically, and growing in number, as shown in Figure 3. Based on our data, we cannot determine the exact reasons for the observed increase in the number of "OAI"-coded inspection findings between 1993 and 1999 (Figure 3) which mostly occurred in the Europe West region. It remains unclear whether that uptick was due to a change in inspection practices, inclusion of new, unexperienced clinical trial sites, or other reasons. However, the reduction of the incidence of "OAI" findings observed in the late 90's coincides time-wise with the adoption of International Conference for Harmonization's harmonised guidelines for Good Clinical Practice in 1996,[15] and shows the possible impact of a harmonized approach on clinical trial quality assurance, which in turn affected inspection outcomes.

For both "VAI" and "OAI" inspection findings, we note that most of these actions were related to documentation and reporting issues. These deficiencies were often due to failure to perform relatively simple tasks, many of which could be improved with better GCP training and trial execution by CROs that supervise most trials. It is also important to note that most of these findings (except for adverse drug reaction reporting deficiencies) are not related to study participants' safety. On the other hand, deficiencies related to improper execution or documentation of the informed consent procedure and adherence to ethical standards may have a serious impact on the patients' personal integrity. Other aspects found were related to quality of trial that may affect study results and, if the study results are skewed, also affect the patients later in the clinical setting when drugs and device are implemented. Another aspect that might affect the difficulties related to documentation and reporting issues is that various CROs often use different case report form (CRF) types, which may affect these fairly simple tasks of documentation as well as affecting trial participant recruitment, making data collection burdensome, and make generalizability of clinical practice uncertain[16]. Documentation and reporting issues may also increase the cost of clinical research[17] and may result in declining investment in the medical field[16]. There are new approaches to clinical trial execution where data are extracted from digital health records. In such instances, clinical trial personnel work with computer systems and programs that they are familiar with, which makes training in different CRF systems unnecessary and may help improve data quality[17-18].

No inspections were conducted after March 2020 (Figure 3). One study showed that many clinical trials were stopped[20] unless they were related to COVID-19 research during this period. Furthermore, travel restrictions in most parts of the world may also explain the difficulty in conducting FDA inspections.

We found that data falsification was an extremely a rare finding. This occurred during just one out of 3,222 inspections conducted outside the US. There are different strategies for treating and reporting data falsification.[22] Steen and his colleague[21] previously evaluated articles that reported on clinical trials conducted between 2000 and 2010. Steen and colleagues found that of 180 retracted articles, there were 9 clinical trials, 7 of which were retracted for fraud.[23] Under the FDA Proposed Rule, the Agency estimates that it will receive 73 reports of data falsification reports annually across its multiple FDA divisions.[21] This reveals that the more inspections are conducted, the higher the number of "OAI" findings reported and falsifications found. This data from FDA may indicate that more international regulatory authorities should make inspection results available for independent review. This will help analyse more robust data, get a better understanding of how clinical trial quality can be improved around the world. We find that the easily-accessible FDA clinical investigator inspection lists deserve greater

attention and follow-up from pharmaceutical companies, CRO's, medical doctors, and study coordinators involved in clinical trials. Notably, while ever more countries are participating in large clinical trials, FDA inspection results seem to remain constant. As referred to above, "OAI" were noted in just 21 of the 77 countries inspected by the FDA.

Conclusion

The US Food and Drug Administration monitors just a small number of all clinical trials conducted worldwide. Despite the great difference in the number of FDA inspections conducted in different regions, the structure of inspection findings is remarkably similar across the globe, with very rare "OAI" findings and GCP violations codes observed. If data from other countries and regulatory authorities around were available, we would gain an even better understanding of clinical investigators' training needs to further improve clinical trial quality standards.

Conflicts of Interest Statement

None of this article's authors have any conflicts of interest concerning this article's topics.

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APPENDIX

Appendix 1. *Dates the FDA started inspections outside the US; by region/country.*

Region	Country	First inspection date
South America	Argentina	1980-01-28
Central America	Mexico	1980-02-11
Australia	New Zealand	1980-08-22
Canada	Canada	1981-05-01
Europe West	United Kingdom	1981-08-21
South America	Venezuela	1983-12-01
Asia	Malaysia	1984-02-24
Europe West	Netherlands	1984-09-11
Europe West	Sweden	1985-03-07
Europe West	Germany	1985-12-04
Europe West	Finland	1987-02-23
Caribbean	Bahamas	1988-03-21
Asia	Japan	1988-12-02
Australia	Australia	1989-03-28
Europe West	Denmark	1990-06-27
Caribbean	Dominican Republic	1990-07-16
Europe West	Italy	1992-03-23
Europe West	Spain	1992-04-02
Europe West	Belgium	1992-10-19
Europe West	France	1992-11-02
Middle East	Israel	1992-12-06
Africa	South Africa	1994-01-17
South America	Brazil	1996-03-04
South America	Peru	1996-05-20
Caribbean	Costa Rica	1996-06-03
Europe East	Ukraine	1996-07-16
Africa	Nigeria	1997-06-16
Central America	Panama	1997-08-25
Asia	Philippines	1997-09-15
Europe West	Austria	1997-12-01
Europe West	Poland	1997-12-08
Europe West	Czech Republic	1998-01-12
Europe West	Hungary	1998-01-19
Europe West	Ireland	1998-07-20
Europe West	Slovakia	1998-08-10
Europe West	Norway	1998-09-07
Europe West	Romania	1998-09-14
Europe West	Portugal	1999-04-26
Africa	Kenya	1999-05-24
Africa	Gabon	1999-05-31
Asia	China	1999-06-07

Europe East	Russia	1999-09-27
Europe West	Switzerland	2000-06-26
Central America	Guatemala	2000-07-31
Europe West	Croatia	2000-08-28
Africa	Malawi	2001-07-30
Asia	Thailand	2001-08-07
South America	Chile	2002-06-10
Europe West	Greece	2002-06-25
Asia	Taiwan	2002-07-08
Africa	Egypt	2002-10-27
Africa	Zambia	2002-11-04
Europe West	Latvia	2003-06-30
Europe West	Lithuania	2003-07-14
Europe West	Estonia	2003-10-13
South America	Colombia	2004-07-26
Europe West	Serbia	2004-11-08
Middle East	Turkey	2005-01-24
South America	Ecuador	2005-03-29
India	India	2005-05-09
Asia	Singapore	2006-05-22
Europe West	Bulgaria	2007-02-05
Asia	South Korea	2007-09-10
Africa	Tanzania	2008-10-20
Asia	North Korea	2009-08-10
North Africa	Morocco	2009-12-07
North Africa	Tunisia	2009-12-14
South America	Paraguay	2010-02-04
Asia	Bangladesh	2010-04-18
Africa	Ghana	2010-04-19
Europe East	Georgia	2011-03-01
Africa	Uganda	2012-04-23
Caribbean	Puerto Rico	2014-12-11
Africa	Gambia	2015-04-01
Africa	Ethiopia	2016-09-19
Europe West	Bosnia and Herzegovina	2017-09-11
Europe East	Belarus	2019-04-01

Appendix 2. *The number of FDA inspections outside the US between January 1980 and October 2021.*

Continents, Countries and Number (%) of inspections (Total=3,222)
Africa: 116 (3.5%)
South Africa: 90 and Others*: 26.
Asia: 239 (7.4%)
China: 49, South Korea: 43, Japan: 42, Thailand: 21, Malaysia: 19, Taiwan: 19, Philippines: 15 and Others*: 8.
Canada: 386 (12.0%)
Europe East: 184 (5.7%)
Russia: 129, Ukraine: 43, Georgia: 10, and Others*: 2.
Europe West: 1,789 (55.5%)
United Kingdom: 241, Germany: 233, France: 199, Poland: 189, Italy: 124, Netherlands: 92, Spain: 90, Belgium: 84, Sweden: 71, Hungary: 70, Czech Republic: 60, Romania: 53, Denmark: 37, Austria: 36, Bulgaria: 29, Finland: 27, Croatia: 27, Serbia: 24, Greece: 19, Latvia: 20, Estonia: 15, Norway: 12, Portugal: 11, Others*: 2.
South America: 240 (7.4%)
Argentina: 93, Brazil: 82, Peru: 25, Chile: 24 and Others*: 16.
Other*: 264 (8.3%)
India: 84, Mexico: 57, Israel: 29, Australia: 31, Costa Rica: 21, Guatemala: 10, Turkey: 11, New Zealand: 10, and Others*: 15.
*Others: **Africa**: Tanzania: 5, Ghana: 4, Malawi: 2, Uganda: 2, Kenya: 2, Nigeria: 2, Morocco: 2, Tunisia: 2, Egypt: 1, Ethiopia: 1, Gabon: 1, Gambia: 1, Zambia: 1. **Asia**: North Korea: 5, Singapore: 2, Bangladesh: 1. **Europe East:** Belarus: 2, **Europe West**: Slovakia: 9, Lithuania: 8, Ireland: 4, Switzerland: 3, Bosnia and Herzegovina: 2. **South America**: Colombia: 6, Paraguay: 4, Venezuela: 4, Ecuador: 2. **Other**: Dominican Republic: 6, Bahamas: 3, Panama: 3, Puerto Rico: 2.

Appendix 3. *Detailed FDA non-US inspection results by classification and deficiencies codes January 1980 - October 2021.*

Classification and deficiency codes		**N 3,222 (%)**
No Action Indicated: No objectionable conditions or practices were found during the inspection.		1,243 (38.6%)
Voluntary Action Indicated (VAI): Objectionable conditions were found, but the problems do not justify further regulatory action. Any corrective action is left up to the investigator to take voluntarily.		1824 (56.6%)
Deficiency Codes VAI		
05	Failure to follow investigational plan	666 (36.5%)
06	Inadequate and inaccurate records	509 (27.9%)
03	Inadequate informed consent form	175 (9.6%)
04	Inadequate drug accountability	143 (7.8%)
16	Failure to report adverse drug reactions	111 (6.1%)
18	Other	58 (3.2%)
02	Failure to obtain and/or document subject consent	41 (2.2%)
NG	Not Given	36 (2.0%)
15	Failure to notify IRB of changes, failure to submit progress reports	28 (1.5%)
01	Records availability	24 (1.3%)

14	Failure to obtain or document IRB approval	13 (0.7%)
07	Unapproved concomitant therapy	8 (0.4%)
12	Failure to list additional investigators on 1670	4 (0.2%)
10	Inappropriate delegation of authority	4 (0.2%)
00	No deficiencies noted	3 (0.2%)
19	Failure to supervise or personally conduct the clinical investigation	1 (0.1%)
Official Action Indicated (OAI): Objectionable conditions were found, and regulatory and/or administrative sanctions by FDA are indicated.		126 (3.9%)
Deficiency Codes OAI		
06	Inadequate and inaccurate records	34 (26.9%)
05	Failure to follow investigational plan	29 (23.0%)
04	Inadequate drug accountability	18 (14.3%)
03	Inadequate informed consent form	13 (10.3%)
18	Other	12 (9.5%)
01	Records availability	6 (4.7%)
02	Failure to obtain and/or document subject consent	5 (3.9%)
16	Failure to report adverse drug reactions	3 (2.3%)
07	Unapproved concomitant therapy	2 (1.6%)
17	Submission of false information	2 (1.6%)
NG	Not Given	2 (1.6%)
Cancelled (CANC)	The inspection was cancelled prior to start.	20 (0.6%)
Washout (WASH)	The inspection was initiated, but no meaningful information could be obtained.	4 (0.1%)

Appendix 4. FDA inspection results re: deficiencies, broken down by non-US regions, January 1980 - October 2021.

Africa (N = 11)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	26 (21.6%)	1 (0.9%)
Failure to obtain and/or document subject consent	5 (4.7%)	0 (0.0%)
Failure to obtain or document IRB approval	3 (2.8%)	0 (0.0%)
Failure to report adverse drug reactions	1 (0.9%)	0 (0.0%)
Inadequate and inaccurate records	13 (11.2%)	2 (1.7%)
Inadequate drug accountability	6 (5.6%)	0 (0.0%)
Inadequate informed consent form	8 (7.5%)	0 (0.0%)
No deficiencies noted	30 (28.0%)	0 (0.0%)
Not Given	16 (15.0%)	0 (0.0%)
Records availability	1 (0.9%)	0 (0.0%)
Unapproved concomitant therapy	1 (0.9%)	0 (0.0%)
Asia (N = 13)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	36 (16.7%)	0 (0.0%)
Failure to list additional investigators on 1670	1 (4.3%)	0 (0.0%)
Failure to notify IRB of changes, failure to submit progress reports	5 (2.3%)	0 (0.0%)
Failure to obtain and/or document subject consent	2 (0.9%)	0 (0.0%)
Failure to obtain or document IRB approval	1 (0.5%)	0 (0.0%)
Failure to report adverse drug reactions	3 (1.4%)	0 (0.0%)
Inadequate and inaccurate records	38 (17.6%)	0 (0.0%)
Inadequate drug accountability	8 (3.7%)	0 (0.0%)
Inadequate informed consent form	14 (6.5%)	0 (0.0%)
Inappropriate delegation of authority	1 (4.3%)	0 (0.0%)
No deficiencies noted	85 (39.3%)	1 (0.3%)

Not Given	20 (9.3%)	0 (0.0%)
Other	3 (1.4%)	0 (0.0%)
Canada (N=16)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	81 (21.0%)	2 (0.5%)
Failure to list additional investigators on 1684	1 (0.3%)	0 (0.0%)
Failure to list additional investigators on 1685	1 (0.3%)	0 (0.0%)
Failure to notify IRB of changes, failure to submit progress reports	3 (0.8%)	0 (0.0%)
Failure to obtain and/or document subject consent	5 (1.3%)	0 (0.0%)
Failure to obtain or document IRB approval	4 (1.0%)	0 (0.0%)
Failure to report adverse drug reactions	14 (3.6%)	0 (0.0%)
Inadequate and inaccurate records	67 (17.4%)	2 (0.5%)
Inadequate drug accountability	23 (6.0%)	0 (0.0%)
Inadequate informed consent form	36 (9.3%)	1 (0.3%)
No deficiencies noted	77 (19.9%)	1 (0.3%)
Not Given	54 (14.0%)	1 (0.3%)
Other	6 (1.6%)	0 (0.0%)
Records availability	5 (1.3%)	1 (0.3%)
Submission of false information	2 (0.5%)	2 (0.5%)
Unapproved concomitant therapy	2 (0.5%)	0 (0.0%)
Europe West (N = 16)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	386 (21.6%)	20 (1.1%)
Failure to list additional investigators on 1692	1 (0.1%)	0 (0.0%)
Failure to notify IRB of changes, failure to submit progress reports	11 (0.6%)	0 (0.0%)
Failure to obtain and/or document subject consent	20 (1.1%)	2 (0.1%)
Failure to obtain or document IRB approval	4 (0.2%)	0 (0.0%)
Failure to report adverse drug reactions	67 (3.7%)	3 (0.2)
Failure to supervise or personally conduct the clinical investigation	1 (0.1%)	0 (0.0%)
Inadequate and inaccurate records	287 (16-0%)	20 (1.1%)
Inadequate drug accountability	83 (4.6%)	15 (0.8%)
Inadequate informed consent form	94 (5.3%)	10 (0.6%)
Inappropriate delegation of authority	3 (0.2%)	0 (0.0%)
No deficiencies noted	488 (27.3%)	0 (0.0%)
Not Given	197 (11.0%)	0 (0.0%)
Other	43 (2.4%)	12 (0.7%)
Records availability	12 (0.7%)	2 (0.1%)
Unapproved concomitant therapy	3 (0.2%)	1 (0.1%)
East Europe (N = 11)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	25 (13.6%)	0 (0.0%)
Failure to notify IRB of changes, failure to submit progress reports	1 (0.5%)	0 (0.0%)
Failure to obtain and/or document subject consent	1 (0.5%)	0 (0.0%)
Failure to report adverse drug reactions	3 (1.6%)	0 (0.0%)
Inadequate and inaccurate records	24 (13.0%)	1 (0.5%)
Inadequate drug accountability	2 (1.1%)	1 (0.5%)
Inadequate informed consent form	2 (1.1%)	0 (0.0%)
No deficiencies noted	85 (46.2%)	0 (0.0%)
Not Given	36 (19.6%)	0 (0.0%)
Other	2 (1.1%)	0 (0.0%)
Records availability	1 (0.5%)	0 (0.0%)
South America (N = 11)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	47 (19.6%)	3 (1.3%)

Failure to notify IRB of changes, failure to submit progress reports	5 (2.1%)	0 (0.0%)
Failure to obtain and/or document subject consent	4 (1.7%)	3 (1.3%)
Failure to report adverse drug reactions	6 (2.5%)	3 (1.3%)
Inadequate and inaccurate records	29 (12.1%)	3 (1.3%)
Inadequate drug accountability	10 (3.3%)	2 (0.8%)
Inadequate informed consent form	12 (5.0%)	0 (0.0%)
No deficiencies noted	78 (32.5%)	0 (0.0%)
Not Given	33 (13.8%)	0 (0.0%)
Records availability	2 (0.8%)	0 (0.0%)
Unapproved concomitant therapy	1 (0.4%)	0 (0.0%)
Others (N = 12)	**VAI N (%)**	**OAI N (%)**
Failure to follow investigational plan	61 (23.1%)	2 (0.8%)
Failure to notify IRB of changes, failure to submit progress reports	2 (0.8%)	0 (0.0%)
Failure to obtain and/or document subject consent	4 (1.5%)	0 (0.0%)
Failure to report adverse drug reactions	6 (2.3%)	6 (2.3%)
Inadequate and inaccurate records	53 (20.1%)	1 (0.4%)
Inadequate drug accountability	12 (4.5%)	1 (0.4%)
Inadequate informed consent form	9 (3.4%)	1 (0.4%)
No deficiencies noted	76 (28.8%)	0 (0.0%)
Not Given	10 (3.8%)	0 (0.0%)
Other	6 (2.3%)	1 (0.4%)
Records availability	3 (1.1%)	3 (1.1%)
Unapproved concomitant therapy	1 (0.4%)	0 (0.0%)

VAI = Voluntary Action Indicated, OAI = Official Action Indicated and N = Number