Comparison of good clinical practice compliance and readability ease of the informed consents between observational and interventional clinical studies in the Emirates

Background: Expansion of clinical trials activity into emerging regions has raised concerns regarding participant rights and research ethics. Increasing numbers of observational studies are now conducted in developing economies, including the United Arab Emirates.

Materials and Methods: This study compares the content of information provided, Good Clinical Practice (GCP) guideline compliance, and readability of informed consent forms (ICFs) for observational compared to interventional studies. Results: GCP compliance for observational studies averaged at 79.5% ± 6.8%, significantly (P < 0.001) lower than 92.2 ± 5.0 percent for interventional studies. Readability ease and readability-grade level were assessed with Flesch-Kincaid scales. Results indicated higher readability grade-level 12.4 ± 0.4 (P < 0.001) and lower readability Flesch-Kincaid reading ease score 35.7 ± 3.6 for observational studies, as compared to 10.3 ± 1.6 and 47.8 ± 7.4 for interventional studies. Conclusion: Mandatory training for investigators is essential to provide readability ease and GCP compliance for the ICFs for the local population.

Key words: Clinical trials, gulf, informed consents, compliance readability

INTRODUCTION

Clinical research studies using human subjects are conducted to examine the efficacy and safety of new drugs, devices and treatments prior to mass production and distribution in the open market. Despite stringent regulations and multiple safeguards, serious adverse events have been identified postapproval.[1] In recent years, the pharmaceutical industry has expanded the scope of observational research studies to include clinical and patient-reported health outcomes.[2] Three main forces drive the conduct of observational research studies, namely the need to obtain treatment information under standard care conditions in the real-world setting; the superiority of the observational study methodology compared to interventional methodologies when large numbers of patients are involved or when long-term follow-up is...
needed; and the potential ethical issues inherent to any large-scale interventional study.\[9\]

In the past decade, there has been a rapid expansion of clinical trials activity into developing countries, including Asia and the Middle East.\[4,5\] This increase has been driven mainly by lower trial costs and larger patient population, particularly in countries with high disease burden and large numbers of treatment-naïve individuals.\[4,5\] Among the Gulf Cooperation Countries (GCC), Saudi Arabia, followed by the United Arab Emirates (UAE), lead the region in the total number of clinical trials conducted annually.\[6\] Thirty-four percent of all registered studies are observational in Saudi Arabia, 37% in the UAE and between 48–65% in Bahrain, Oman, Qatar, and Kuwait [Table 1].\[6\] Comparatively, similar emerging economies of Asia and the non-GCC Arab countries have 11–20% of the total as observational studies [Table 1].

The rapid increase in clinical trials in emerging countries has raised concerns regarding participant rights and research ethics.\[7,8\] Globally, the informed consent process is a required part of all clinical research, and the informed consent form (ICF) is a critical part of the process.\[9\] There is a large body of literature that addresses both the need for the ICF, as well as the difficulties posed by this often lengthy and technical document.\[9\] In established markets, national regulatory agencies oversee the clinical trial conduct and ICF compliance.\[10,11\] Emerging markets often follow the recommendations of the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) in the development of ICF structure and content.\[10\] However, the ICH-GCP assigns much of clinical trial oversight and monitoring to the local Institutional Review Board (IRB).\[12\]

More than three-quarters (76%) of interventional studies and less than half (42%) of all observational studies conducted in the UAE are sponsored by the pharmaceutical industry.\[1\] Good Clinical Practice (GCP) compliance for ICFs from industry-sponsored studies in the UAE has been reported to be >80%.\[13\] Despite the large number of observational studies conducted in the UAE annually, evidence regarding the structure and content of information provided in the ICF and compliance with international GCP guidelines for observational studies is lacking. These questions encouraged the authors to investigate the nature of information provided in the ICF from observational studies as compared to interventional studies, and further assess the readability of the ICF between these two types of studies conducted in the UAE.

| Table 1: Percentage of observational research studies registered at clinicaltrials.gov with respect to the total number of registered studies. Emerging clinical trial markets such as Asia and Middle East exhibit lower percentage of observational studies. Greater than 50% of registered studies are observational for GCC countries except Saudi Arabia (34%) and UAE (37%) |
|---|---|---|---|
| **Countries** | **Number of observational research studies** | **Total number of registered studies** | **Observational studies as % of total** |
| GCC | | | |
| Bahrain | 11 | 17 | 65 |
| Kuwait | 26 | 49 | 53 |
| Oman | 10 | 21 | 48 |
| Qatar | 25 | 49 | 51 |
| Saudi | 108 | 321 | 34 |
| Arabia | | | |
| UAE | 39 | 105 | 37 |
| Middle East | | | |
| Egypt | 117 | 676 | 17 |
| Iran | 59 | 475 | 12 |
| Jordan | 89 | 561 | 16 |
| Lebanon | 247 | 1811 | 15 |
| Asia | | | |
| China | 1164 | 5944 | 20 |
| India | 294 | 2704 | 11 |
| Japan | 504 | 3732 | 14 |

UAE=United Arab Emirates, GCC=Gulf Cooperation Countries

**METHODS**

The ICH-GCP informed consent guidelines suggest the inclusion of 20 informational items in the ICF.\[13,14\] These guidelines have been adopted by local UAE regulatory agencies.\[13,16\] Following ethics approval (#12/55) and a confidentiality disclosure agreement with the regional Research Ethics Committee (REC) to protect the identities of the studies and participants, a multicenter retrospective cross-sectional analysis of 159 ICFs was conducted at two Joint Commission-International Accredited Tertiary Care Centers in the Emirate of Abu Dhabi, UAE. Study protocols containing ICFs from all interventional and observational studies involving human participants submitted for initial (first) review to the REC between January 2009 and May 2014 were considered eligible.\[14\] Both industry sponsored and nonsponsored studies were included. Fourteen informational items [Figure 1] common to both interventional and observational studies were compared with a standard ICH-GCP-ICF template, and the information was coded as “informational item present” or “informational item absent” by a multilingual physician-investigator blinded to the study hypothesis and further verified by a second physician rater.\[17,18\] ICF information that was in accordance with the standard GCP requirements was recorded as “informational item present” and scored as +1. If an item was completely
absent or partially present, it was labeled as “informational item absent” and scored as 0.17,18 A minimum score of 0 points and maximum score of 14 points were possible for each ICF.14 In addition, a readability test was applied to all 159 ICFs. The Flesch-Kincaid readability scale was chosen because of its convenience for computerized use, reproducibility, and superior correlation with other established readability scales.19 The Flesch-Kincaid grade level formula then translates the score to a grade level, indicating the number of years of education generally required to understand a given text.19 Data were statistically analyzed using SPSS (IBM 20.0) and expressed as percentage or as mean ± standard deviation (SD). A P < 0.05 was considered statistically significant. Inter-rater reliability was determined using Cohen’s kappa.20

RESULTS

Informed consent forms from several therapeutic areas, including cardiovascular disease, diabetes, infectious disease, oncology, renal disease, and women’s health, constituted the 159 consent forms reviewed. GCP compliance for interventional studies averaged at 92.2% ± 5.0%, while GCP compliance for observational studies was only 79.5% ± 6.8% (P < 0.001) [Figure 1]. Less than 75% of the ICFs from observational studies included informational items, such as number of visits required, duration of participation, participant rights/responsibilities, voluntary participation, and withdrawal. Interestingly, ICFs from sponsored observational studies showed improved GCP compliance (84.7% ± 10.2%) when compared to their nonsponsored counterparts (77.3% ± 8.9%) (data not shown).

The Flesch-Kincaid readability test was also applied to all 159 ICFs from observational and interventional studies. The mean ± SD Flesch-Kincaid Grade Level Score for the ICFs from interventional studies was 10.3 ± 1.6, significantly lower than 12.4 ± 0.4 (P < 0.001) for observational studies. The mean ± SD FRES score for the ICFs from interventional studies was 47.8 ± 7.4 (n = 47), significantly higher (P < 0.001) than 35.7 ± 3.6 (n = 112) for nonsponsored interventional studies (P < 0.001) [Table 2].

Better readability is associated with a higher FRES Score.19 It is important to note that none of the ICFs reviewed, irrespective of whether interventional or observational, met the criteria for standard readability [Figure 2] per the standard readability assessment scale.19 The ICFs reviewed from interventional studies were almost evenly distributed between the “difficult” (47%) and “fairly difficult” (53%) range of readability. ICFs from all observational studies reviewed (100%) were in the “difficult” category for readability [Figure 2]. Cohen's kappa coefficient, a measure of inter-rater (two raters) agreement, was high between k = 0.7–0.73 for the readability assessment and GCP compliance review of the ICFs from all the studies.

DISCUSSION

Increasing interest in the conduct of clinical trials in the UAE has recently been reported, primarily driven by

### Table 2: FRES and corresponding FGLS was employed to assess readability ease of the informed consent forms from interventional and observational studies

| Categories               | FRES       | FGLS       |
|--------------------------|------------|------------|
| Interventional (n=47)    | 48.7±7.4*  | 10.3±1.6*  |
| Observational (n=112)    | 35.7±3.6   | 12.4±0.4   |

*(P<0.002). FRES=Flesch-Kincaid Readability Ease Score, FGLS=Fresch-Kincaid Grade Levels

*Figure 1: Good Clinical Practice (GCP) compliance Assessment: One hundred fifty-nine informed consent forms from observational and interventional studies from various therapeutic areas were reviewed for GCP compliance

*Figure 2: Standard readability assessment: None of the consent forms reviewed, irrespective of whether interventional or observational, met the criteria for standard readability per the standard readability assessment scale. The informed consent forms (ICFs) reviewed from interventional studies were almost evenly distributed between the “difficult” (47%) and “fairly difficult” (53%) range of readability. ICFs from all observational studies reviewed (100%) were in the “difficult” category for readability
lower operational costs, modern health-infrastructure, and the country’s relatively high prevalence of metabolic disorders.\[14,21,22\] The increasing presence of major pharmaceutical sponsors, especially in Abu Dhabi and Dubai, is a reflection of recent government initiatives to promote medical research.\[5\] Similar to the trend observed in other GCC countries, observational studies constitute more than one-third of the total sponsored clinical trials by pharmaceutical companies in the UAE [Table 1]. In this study, overall GCP compliance of the ICFs was noted to be significantly lower for observational studies than for interventional trials. A vast majority (76%) of interventional studies conducted in the UAE are industry-sponsored and a part of global trials. The reason for higher GCP compliance for the ICFs from interventional trials in the UAE can be attributed to the meticulous development of study protocol, ICFs and related material by the pharmaceutical industry for sponsored global studies. On the contrary, a sizable number of observational studies are predominantly initiated by investigators in the UAE. Many previous studies in the West have documented that ICFs used, in general, medical research are increasingly long, complex, and difficult for the general population to understand.\[23,24\] In the USA, standard legal documents are expected to be written at an eighth-grade reading level.\[23\] In the multiethnic, multicultural UAE, where many study participants are nonnative English (or Arabic) speakers, the readability of the ICF is of even greater concern. In our study, the average reading level of the ICFs reviewed ranged between 10\(^{th}\) grade reading level for interventional research studies and 12\(^{th}\) grade reading level for observational studies. The readability issues likely stem from the fact that the majority of ICFs, especially those from nonsponsored observational studies, are home-grown, developed by the investigators themselves and their study teams, who may not be adequately trained. Health authorities, regulators of health and health research in the UAE, rely on the local IRBs for clinical trial oversight and monitoring. However, local IRBs may lack both training and resources to conduct oversight.

It is only within the past 5 years that the availability of internationally trained healthcare professionals and evolving regulatory framework in the UAE has enabled the country to become a promising destination for clinical trials.\[5\] Although clinical research studies are, thereby, relatively new to the UAE, issues with GCP compliance and readability of the ICFs are quite similar to those observed globally.\[25\] This is, to our knowledge, the first study in the region that has compared GCP compliance and readability of ICFs between interventional and observational studies. Our findings should be viewed in light of several limitations. First, it is possible that all observational studies may not be registered on international portals, such as ClinicalTrials.gov, especially when there are no regulations in the UAE that require trial registration. Our studies, however, were identified directly through the REC, without reliance on national registries. Furthermore, issues related to registration of clinical trials are common to both developed and emerging markets. Further, ICFs reviewed were from two academic medical centers and may not be representative of all studies performed in the country. This limitation is partially alleviated by the fact that these two institutions conduct the largest number of clinical research studies in the UAE annually. Further, data items either partially or completely absent were both scored as “zero” possibly leading to skewed data for compliance. As <3% (2.67%) of observational studies showed the partial presence of essential information, it is unlikely that employing this methodology had any significant effect on compliance outcomes. Finally, readability of the ICFs was assessed for this study, but not comprehension by the research subjects. Health literacy rates in the UAE, especially for the elderly and the unskilled expatriate workers, are currently unknown. This is an important area for future research.

In summary, our results highlight deficiencies in GCP compliance and readability ease of the ICFs from observational studies. Given the legal and ethical importance of obtaining informed consent from research participants, investigator, and IRB members training should be prioritized. Locally developed ICF templates that have been piloted on laypersons in the local population to assess readability ease may improve GCP-ICH compliance. Career advancement and protected time for IRB members may help improve their commitment to IRB activities. Creating public awareness about clinical research, development of electronic applications, as well as visual graphics that could reduce ICF length and complexity, are all potential solutions to reduce the readability issues related to the ICFs for the local population.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES
1. Bajpai V, Saraya A. Boom in clinical research industry: A dangerous trend. Trop Gastroenterol 2009;30:177-81.
2. Langham S, Langham J, Goertz HP, Ratcliffe M. Large-scale, prospective, observational studies in patients with psoriasis and psoriatic arthritis: A systematic and critical review. BMC Med Res Methodol 2011;11:32.
3. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342:1878-86.
4. Patel VH, Kirkwood BR, Pednekar S, Araya R, King M, Chisholm D, et al. Improving the outcomes of primary care attenders with common mental disorders in developing countries: A cluster randomized controlled trial of a collaborative stepped care intervention in Goa, India. Trials 2008;9:4.

5. Nair SC, Ibrahim H, Coletano DD. Clinical trials in the Middle East and North Africa (MENA) Region: Grandstanding or grandeur? Contemp Clin Trials 2013;36:704-10.

6. Clinicaltrials.gov. Available from: http://www.clinicaltrials.gov. [Last accessed on 2014 Nov 21].

7. Bristol N. US reviews human trial participant protections. Lancet 2010;376:1975-6.

8. Mandava A, Pace C, Campbell B, Emanuel E, Grady C. The quality of informed consent: Mapping the landscape. A review of empirical data from developing and developed countries. J Med Ethics 2012;38:356-65.

9. Beecher HK. Ethics and clinical research. N Engl J Med 1966;274:1354-60.

10. Dixon JR Jr. The International Conference on Harmonization Good Clinical Practice guideline. Qual Assur 1998;6:65-74.

11. Irumnaz A, Nair SC. Clinical trials in Pakistan: Opportunities and challenges. Appl Clin Res Clin Trials Regul Aff 2014;1:23-7.

12. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. J Infect Dis 2004;189:930-7.

13. ICH-GCP. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: ICH Harmonized Tripartite guideline, second step 4 Version; 2010, p. 1-26. Available from: http://www.fda.gov/ohrms/dockets/ac/02/briefing/08376b1_03_ICH%20e9.pdf. [Last accessed on 2015 Jan 03]

14. Nair SC, Ibrahim H. Informed consent form challenges for genetic research in a developing arab country with high risk for genetic disease. J Genet Couns 2015;24:294-9.

15. Ibrahim K, Eada EA, Younis N. Guidelines Ministry of Health-Drug control-UAE guidance for conducting clinical trials based on drugs/medical products and good. clin Pract 2006;6:1-44.

16. HAAD; 2006. Available from: http://www.haad.ae. [Last accessed on 2014 Nov 29].

17. Falagas ME, Korbila IP, Giannopoulou KP, Kondilis BK, Peppas G. Informed consent: How much and what do patients understand? Am J Surg 2009;198:420-35.

18. Resnik DB, Patrone D, Peddada S. Evaluating the quality of information about alternatives to research participation in oncology consent forms. Contemp Clin Trials 2010;31:18-21.

19. Terblanche M, Burgess L. Examining the readability of patient-informed consents. J Clin Trials 2010;2:157-62.

20. Viera AJ, Garrett JM. Understanding interobserver agreement: The kappa statistic. Fam Med 2005;37:360-3.

21. Barakat-Haddad C. Prevalence of high blood pressure, heart disease, thalassemia, sickle-cell anemia, and iron-deficiency anemia among the UAE adolescent population. J Environ Public Health 2013;2013:680631.

22. Ibrahim H, Awadhi AA, Shaban S, Nair SC. Can our residents carry the weight of the obesity crisis? A mixed methods study. Obes Res Clin Pract 2014; Oct 19. pii: S1871-403X(14)00545-6. doi: 10.1016/j.orcp.2014.09.004. [Epub ahead of print] PMID: 25458373

23. Richardson V. Patient comprehension of informed consent. J Perioper Pract 2013;23:26-30.

24. Joffe S, Cook EF, Cleary PD, Clark JW, Weeks JC. Quality of informed consent: A new measure of understanding among research subjects. J Natl Cancer Inst 2001;93:139-47.

25. Bansal N. The Opportunities and challenges in conducting clinical trials globally. Clin Res Regul Aff 2012;29:9-14.