JACOBS PUBLISHERS

OPEN ACCESS

Concise Review

Improving and Preventing Lapse in Institutional Review Board Continuing Review Approval

Min-Fu Tsan[1*], M.D., Ph.D., and Linda W. Tsan[1], M.D.

[1]*McGuire Research Institute and Veterans Affairs Medical Center, Richmond, VA, USA*

**Corresponding author: Dr. Min-Fu Tsan, M.D., Ph.D.,718 Hawkins Way, Alexandria, VA 22314, USA, Tel: 703-836-3793; Email: minfu.tsan@gmail.com*

Received: 11-05-2017

Accepted: 11-21-2017

Published: 11-25-2017

Abstract

Continuing review of on-going research is one way by which institutional review boards (IRBs) ensure the protection of human subjects participating in clinical trials. However, little is known about the prevalence of lapse in IRB continuing reviews, factors that may contribute to it, and measures to prevent its occurrence. Analysis of the United States Department of Veterans Affairs (VA) research facility's IRB continuing review performance metric data revealed that lapse in IRB continuing reviews was the most commonly identified noncompliance, with lapse rates of 6-7% over a 4-year period from 2010 through 2013. However, investigators from less than 3% of lapsed protocols continued research activities during the lapse. The types of IRB used and the sizes of human research programs had no correlation with the facility's IRB continuing review lapse rates. While 60% of facilities had no lapse in IRB continuing reviews, approximately 20% of facilities had lapse rates of >10% each year. High IRB continuing review lapse rates could be readily improved by implementing measures such as tracking expiration dates of IRB approval; notifying investigators at least 60 days prior to approval expiration; investigator training and education; follow-up with investigators to ensure that continuing review applications were submitted in time for IRB review; and stopping all research activities when lapse occurs. Future studies should be directed toward defining the most cost-effective approaches to prevent and improve lapse in IRB continuing reviews.

Keywords: Human Subjects Protection; Institutional Review Board; Continuing Review

Introduction

Protection of human research subjects is an ethical mandate for all contemporary clinical trials. Continuing review of on-going research is one way by which institutional review boards (IRBs) ensure that human subjects participating in research are adequately protected. It is through continuing reviews that IRBs determine whether research is conducted according to the approved protocols, adverse events are properly reported, and risks to subjects remain reasonable relative to anticipated benefits from the research [1-3].

Despite its importance, scant research focuses on IRB continuing reviews. Little is known about the prevalence of lapse in IRB continuing reviews, factors that may contribute to it, and measures that IRBs may take to prevent or improve lapse in IRB continuing reviews.

We conducted a review of the literature on IRB continuing reviews. The literature search included the United States National Library of Medicine PubMed database and a web search for federal regulations and guidance on IRB continuing reviews. The data were analyzed for the requirements of IRB continuing reviews, the frequency and factors affecting lapse in IRB continuing reviews, and measures that had been shown to improve or prevent a lapse in IRB continuing reviews.

IRB continuing review requirements

The U.S. Federal Policy for the Protection of Human Subjects, also known as the Common Rule, requires that IRBs conduct continuing review of human research at intervals appropriate to the degree of risk, but not less than once per year. Institutional review boards must maintain and follow written procedures for conducting continuing reviews of research projects. In order to re-approve research protocols at continuing

reviews, IRBs must ensure that the research has satisfied all eight Common Rule criteria: minimization of risks to human subjects, reasonable risk to benefit ratio, equitable selection of subjects, requirement of informed consent, documentation of informed consent, monitoring of subject safety, maintaining subject privacy and confidentiality of data, and additional safeguards for vulnerable subjects when appropriate [2,3].

In 1995, Nightingale reported that one of the most common deficiencies identified by the Food and Drug Administration (FDA) was an inadequate or late review of active research protocols [4]. A 1996 Government Accountability Office report also noted that IRB continuing reviews were typically either superficial or not done at all [5]. It was speculated that the underlying cause of this deficiency was that many IRBs were overworked and under-supported by their institutions. A more recent review of 52 warning letters issued to IRBs by FDA from 1997 through 2003 revealed that 36 warning letters (69%) cited IRBs for failure to provide adequate continuing reviews of research protocols [6]. The problem with IRB continuing reviews did not appear to be unique to the United States. In 2008, Norton and Wilson reported that 13% of Canadian research ethics boards did not conduct continuing ethics review of approved studies, even though the Canadian Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans required that at a minimum the research ethics boards should review an annual report submitted by the researcher [7]. Thus, inadequate and/or lapse in IRB continuing reviews appear to be a major problem in human research protections. However, none of these studies provided actual rates of a lapse in IRB continuing reviews.

tion to the IRB or fail to submit applications in time for the IRB to review and reapprove prior to the IRB approval expiration date, and/or IRBs fail to conduct continuing reviews and reapproved the research by the expiration date of IRB approval. Federal regulations do not allow for any grace period extending the conduct of research beyond the expiration date of IRB approval[2,3].

Thus, when lapse in IRB continuing review approval occurs, all research activities involving human subjects must stop, unless the IRB determines that it is in the best interests of subjects who are already enrolled in the study, to continue participating in the research. Under this circumstance, new subjects may not be enrolled, and continuing participation of those already enrolled may be appropriate only when the research interventions hold out the prospect of direct benefit to the subjects or when withholding those interventions poses increased risk to them [2,3] .

Since 2010, the Department of Veterans Affairs (VA) Health Care System has collected and published quality indicator data, including IRB continuing review performance metric data, from its 108 research facilities as part of its human research protection quality assurance program [1,8-10]. A review of the literature revealed that no other institutions have published any IRB continuing review performance metric data.

Of the 25 VA human research protection program performance metrics collected annually from 2010-2013, lapse in IRB continuing review approval had the highest noncompliant rate [1,9].

Table 1. Lapse in institutional review board continuing review approval.

	2010	**2011**	**2012**	**2013**	**p Value[a]**
Total number of facilities	107	107	107	108	
Total number of protocols audited requiring Continuing reviews	1,606	2,942	3,411	3,112	
Lapsed in IRB continuing reviews	97 (6.04%)[b]	208 (7.07%)	209 (6.13%)	189 (6.07%)	0.4173
Continued research activities during lapse	2 (2.06%)[c]	6 (2.88%)	4 (1.91%)	3 (1.58%)	0.4302

[a]Determined by Mantel-Haenszel chi-square test for trend.

[b]The number in parentheses are the percentage of the total number of protocols audited.

[c]The number in parentheses are the percentage of the total number of protocols with lapse in IRB continuing reviews

Lapse in IRB continuing review approval

Lapse in IRB continuing review approval occurs when investigators fail to provide required continuing review applica-

As shown in Table 1, lapse rates of IRB continuing reviews remained relatively constant at 6% to 7% from 2010 through 2013. However, in less than 3% of lapsed protocols, investigators continued research activities, excluding those ac-

tivities that were deemed by the IRBs to be in the best interest of already-enrolled subjects, during the lapses [1,9].

Comparing facilities using own VA IRBs, other VA IRBs, or affiliated university IRBs, there were no statistically significant difference in IRB continuing review lapse rates (Table 2) [1,9].

ments for continuing review are met by the approval expiration date; and IRBs should develop administrative procedures, such as computerized tracking systems, to minimize any unintended expiration of IRB approval [3] .

Ten VA research facilities with IRB continuing review lapse rates that were higher than the VA national average for 3

Table 2. Lapse in continuing reviews according to types of institutional review board used[a].

	Own VA IRBs	Other VA IRBs	Affiliate IRBs
Number of facilities	47.8 (±5.6)	12.3 (±2.5)	31.8 (±1.5)
Lapse rates	6.33% (±1.30%)[b]	6.39% (±4.47%)	6.43% (±1.01%)

[a]Results are expressed as mean(±SD) of data from 2010 to 2013.

[b]p values: 0.9835 (own VA IRB vs. other VA IRB); 0.9139 (own IRB vs. affiliate IRB); and 0.9858 (other VA IRB vs. affiliate IRB)

Likewise, comparing facilities with different sizes of human research programs, there were no statistically significant difference in IRB continuing review lapse rates (Table 3) [1,9]. Thus, neither the types of IRBs used, nor the sizes of human research programs, had any effects on the lapse rate of IRB continuing reviews.

consecutive years from 2011 to 2013, developed and implemented remedial action plans to improve their IRB continuing review lapse rates. Eight of these 10 facilities showed markedly improved lapse rates in IRB continuing reviews after implementing remedial action plans. The mean lapse rate of these 8 facilities was 28.5% (± 13.9%, SD) in 2013 prior to the

Table 3. Lapse in institutional review board continuing reviews according to program sizes[a].

	Small (<50 protocols)	Medium (50-200 (protocols)	Large (>200 protocols)
Number of facilities	27.2 (±2.2)	35.2 (±3.0)	29.3 (±3.9)
Lapse rates	3.99% (±1.78%)[b]	7.30% (±1.30%)	6.12% (±1.66%)

[a]Results were expressed as mean (±SD) of data from 2010 to 2013.[b]*p* values: 0.0221 (small vs. medium); 0.1245 (small vs. large); and 0.2973 (medium vs. large). [Student's t test with Bonnferoni correction for multiple comparisons was used to determine the level of significance. After Bonferroni correction for multiple comparison (n = 3), in order to be considered statistically significant, p value needs to be < 0.017)].

Analysis of facilities with various lapse rates revealed that approximately 60% of facilities had no lapse in IRB continuing reviews, while approximately 20% of facilities had lapse rates of >10% each year (Table 4). In addition, a number of facilities appeared to be repeat offenders. Ten facilities (9.2%) had lapse rates of >10% in 3 or 4 years from 2010 through 2013, suggesting a system problem in these facilities' IRB continuing review approval processes [1,9] .

implementation of remedial action plans, while it was 6.7% (± 8.6%) in 2014 after the implementation (p = 0.0017). The other two facilities failed to fully implement their remedial action plans and did not show any improvement [10].

Remedial measures that these 8 facilities found to be most effective in improving lapse rates of their IRB continuing reviews, included: tracking expiration dates of IRB approval; notifying investigators at least 60 days prior to approval expiration;

Table 4. Number of facilities with various institutional review board continuing review lapse rates[a].

	Lapse rate (0%)	Lapse rate (>0%-10%)	Lapse rate (>10%)
Number of facilities	55 (±6.4))	17 (±7.3)	19.8 (±3.8)
Percent	60.2% (±7.7%)	18.3% (±7.3%)	21.5% (±3.4%)

[a]Results were expressed as mean (±SD) of data from 2010 to 2013.

Improving and preventing lapse in IRB continuing reviews

To avoid lapse in IRB continuing reviews, the Office for Human Research Protections of the Department of Health and Human Services recommends that IRBs and investigators plan ahead to ensure that continuing review and re-approval of research occurs prior to the end of the approval period specified by the IRB; IRB's written procedures should provide for sufficient advance notice to the investigator to ensure that the requirements for continuing review are met by the approval expiration date; and IRBs should develop administrative procedures, such as computerized tracking systems, to minimize any unintended expiration of IRB approval [3] .

investigator training and education; follow-up with investigators to ensure that continuing review application was submitted in time for IRB review; and stopping all research activities when lapse occurs [10] .

Discussion

Considerable efforts have been made to improve the protection of research subjects since early 2000 [11]. However, despite

stronger federal oversight of research, increased institutional support for IRBs, and improved training for investigators and IRB members, a lapse in IRB continuing reviews remains one of the most commonly identified noncompliance. Contrary to the popular belief that lapse in IRB continuing reviews occurs primarily in institutions with large research programs, it occurs in institutions with small and large research programs at roughly the same rates. Likewise, it occurs in equal frequencies in facilities using VA IRBs and facilities using university IRBs as their IRBs of record. As the majority of facilities do not have a lapse in IRB continuing reviews, efforts should be focused on those facilities with high lapse rates [1,9].

Evidence suggests that implementing the following measures will effectively prevent or improve lapses in IRB continuing review approval: 1) establishing a system to track IRB approval expiration dates, preferably using a web-based system with the capability of sending expiration reminders to investigators automatically; 2) notifying investigators at least 60 days prior to the IRB approval expiration date, and staggered thereafter, for example, at 30 and 7 days before IRB approval expires; 3) following up with investigators to ensure that continuing review applications with all required information are submitted in time for IRB review prior to the expiration date; 4) ensuring that all research activities, except those activities that are determined by the IRB to be in the best interest of the already enrolled subjects, stop when lapse in IRB continuing review approval occurs; and 5) educating investigators on the requirement for IRB continuing reviews and the consequence of lapse in IRB continuing review approval, as descirbed in detail previously [10]. Thus, the importance of collaboration between IRB and investigators in ensuring timely IRB continuing reviews cannot be over emphasized.

The above-proposed measures appear quite extensive and may be costly to implement. Future research should be directed to further define the most cost-effective strategy to prevent and improve lapse in IRB continuing reviews.

Performance measurement has been well recognized as an important tool for improving the quality of health care because it identifies areas where quality improvement efforts should be directed [12]. Each year health care providers and payers devote substantial resources to collect, analyze, and report data on providers' performance. One area lagging behind in performance measurement is the protection of human subjects participating in research, particularly the performance of IRBs. The VA experience in IRB continuing review performance measurement, as summarized in this concise review, supports the importance and utility of measuring IRB performance.

Acknowledgement

This research did not receive any specific grant support from any funding agencies in the public, commercial, or not-for-profit sectors.

Disclaimer

The views presented in this review are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

References

1. Tsan MF, Nguyen Y. Lapse in institutional review board continuing review approval. IRB. 2015, 37(2): 14-19.

2. Department of Health and Human Services. Federal Policy for the Protection of Human Subjects. 45 Code of Federal Registration (CFR) 46. 1991.

3. Department of Health and Human Services. Office for Human Research Protections Guidance on IRB Continuing Review of Research. 2010.

4. Nightingale SL. An update from FDA. Plenary address at PRIM&R IRB Conference, 20 October 1995. Boston, Massachusetts.

5. Government Accountability Office. Scientific Research – Continued Vigilance Critical to Protecting Human Subjects. GAO/HEHS-96-72. 1996.

6. Bramstedt KA, Kassimatis K. A study of warning letters issued to institutional review boards by the United States Food and Drug Administration. Clin Invest Med. 2004, 27(6): 316-323.

7. Norton K, Wilson DM. Continuing ethics review practices by Canadian research ethics boards. IRB. 2008, 30(3): 10-14.

8. Tsan MF, Nguyen Y, Brooks R. Using quality indicators to assess human research protection programs at the Department of Veterans Affairs. IRB. 2013, 35(1): 10-14.

9. Tsan MF, Tsan L. Assessing the quality of human research protection programs to improve protection of human subjects participating in clinical trials. Clin Trials. 2015, 12(3): 224-231.

10. Nugyen Y, Grabenbauer M, Tsan MF. Improving rates of lapse in IRB continuing review: The Department of Veterans Affairs' experience. IRB 2016, 38(4): 7-10.

11. Steinbrook R. Improving protection for research subjects. N Engl J Med. 2002, 346(18): 1425–1430.

12. Cassel CK, Conway PH, Delbanco SF, Jha AK, Saunders RS, Lee TH. Getting more performance from performance measurement. N Engl J Med. 2014, 371(23): 2145-2147.