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Monitoring for Adverse Events Post Marketing Approval of a Drug

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Abstract

This brief communication provides information to those developing monitoring plans for serious adverse events (SAE's) following regulatory approval of a new drug. In addition, we (1) illustrate how many patients would need to be treated in order to have high confidence of seeing at least 1 pre-specified SAE, (2) show that absence of proof of a SAE is not proof of absence of that SAE, and (3) identify statistical methodology that could be used for formal statistical monitoring of SAE's.

Introduction

Regardless of the efforts of a pharmaceutical company and of the US Food and Drug Administration (FDA) to identify harmful side effects prior to regulatory approval of a new drug, it is not possible to identify all such serious adverse events (SAE's). There are many reasons for this; chief among them is the fact that the number of patients in clinical development programs of new drugs to prove efficacy are inadequate to detect rare SAE's. It is therefore in a company's best interest to develop a post marketing risk based monitoring plan (RBMP) of their drug as it is made available to patients through physician prescriptions after regulatory approval.

In developing a post marketing RBMP for a specific drug, discussions with the FDA are helpful and essential as are FDA Guidelines regarding a RBMP. The first four references of this document provide links to relevant FDA documents. There is a document [1] that identifies postmarketing requirements and commitments. Some of the studies listed may be required; others may be clinical trials a sponsor has committed to conduct – often conditional on approval.

Another document [2] discusses postmarketing surveillance programs, which include clinical trials conducted after regulatory approval to gather additional information on safety as well in some cases specific questions of efficacy. The FDA maintains a system of postmarketing surveillance and risk assessment programs to identify adverse events (AE's) that did not appear prior and during the drug approval process. FDA monitors AE's and uses the information collected to update drug labeling – and on some occasions to reevaluate the approval or marketing decision.

Another document [3] represents current thinking of the FDA on guidance for industry oversight of clinical investigations from a risk-based approach to monitoring. The guidance does not create or confer any rights for or on any person and does not operate to bind FDA or the public. A company can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If the company wants to discuss an alternative approach, they may contact the FDA staff responsible for implementing the guidance. If the company cannot identify the appropriate FDA staff, they may call the appropriate number listed on the title page of the guidance.

Yet another document [4] describes the FDA Adverse Event Reporting System (FAERS) which is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance [5] issued by the International Conference on Harmonisation ICH E2B. Adverse events and medication errors are coded to terms in the medical dictionary for regulatory activities (MEDRA) [6] terminology.

Executing a RBMP for a newly approved drug will require summarization of individual AE's, particularly SAE's as they accumulate. Table 1, table 2 and table 3 provide relevant information about AE's.

Number of Treated Patients needed to have High Confidence of observing at least 1 AE

Table 1 gives the number of patients that would need to be treated with a drug in order to have $100(1 - \alpha)\%$ confidence of observing at least (\geq) 1 occurrence of a specific AE given that the true AE rate among treated patients is P.

For example, if the fraction of a population who would develop an adverse event upon treatment with a drug at a given dose were 0.1%, one would require 4,604 (Table 1) patients to be treated with the drug at the given dose in order to have 99% confidence of observing at least one patient with the adverse event. If one required a greater degree of certainty, say 99.99%, about 10,000 patients would need to be treated.

Table 1: Number of Patients requiring Treatment with a Drug to have 100(1 - α)% Confidence of Observing at least (\geq) 1 AE given the true AE rate is P

P \ (1- α)	0.90	0.95	0.99	0.999	0.9999
0.001	2302	2995	4604	6906	9208
0.005	460	599	920	1380	1840
0.01	230	300	460	690	920
0.015	153	200	306	459	612
0.02	114	149	228	342	456
0.03	76	99	152	218	304
0.04	57	75	114	171	228
0.05	45	59	90	135	180
0.06	38	50	76	114	152
0.07	32	42	64	96	128
0.08	28	37	56	88	112
0.09	25	33	50	75	100
0.10	22	29	44	66	88
0.15	15	20	30	45	60
0.20	11	15	22	33	44
0.30	07	10	14	21	28
0.40	05	07	10	15	20
0.50	04	06	08	12	16

Table 2: Exact Confidence intervals (95% & 99% CI) on true incidence (P) of a Rare SAE under various scenarios; n = number treated, nP = expected number of SAEs, P (X \geq 1) = Probability of at least 1 SAE among n patients; Outcome = probable number of SAEs among n patients.

P	n	nP*	P(X \geq 1)	95% CI	99% CI	Outcome
.001	25	0	0.025	(0;0.1372)	(0;0.1910)	0
	50	0	0.049	(0;0.0711)	(0;0.1005)	0
	100	0	0.095	(0;0.0362)	(0;0.0516)	0
	150	0	0.139	(0;0.0243)	(0;0.0347)	0
	250	0	0.221	(0;0.0146)	(0;0.0210)	0
	500	0	0.394	(0;0.0074)	(0;0.0105)	0
	1000	1	0.632	(0;0.0037)	(0;0.0053)	0
	1000	1	0.632	(0;0.0056)	(0;0.0074)	1
	10,000	10	0.99996	(0;0.0004)	(0;0.0005)	0
	10,000	10	0.99996	(0.0002;0.0012)	(0.0001;0.0014)	5
	10,000	10	0.99996	(0.0005;0.0018)	(0.0040;0.0021)	10

Table 3: Exact Confidence intervals (95% & 99% CI) on true incidence (P) of a Rare SAE under various scenarios; n = number treated, nP = expected number of SAEs, P (X \geq 1) = Probability of at least 1 SAE among n patients; Outcome = probable number of SAEs among n patients.

P	n	nP*	P(X \geq 1)	95% CI	99% CI	Outcome
.005	25	0	0.118	(0;0.1372)	(0;0.1910)	0
	50	0	0.222	(0;0.0711)	(0;0.1005)	0
	100	0	0.394	(0;0.0362)	(0;0.0516)	0
	150	0	0.529	(0;0.0243)	(0;0.0347)	0
	150	0	0.529	(0;0.0366)	(0;0.0485)	1
	250	1.25	0.714	(0;0.0146)	(0;0.0210)	0
	250	1.25	0.714	(0.0001;0.0221)	(0;0.0293)	1
	500	2.50	0.918	(0;0.0074)	(0;0.0105)	0
	500	2.50	0.918	(0.0001;0.0111)	(0;0.0148)	1
	500	2.50	0.918	(0.0005;0.0144)	(0.0002;0.0184)	2
	1,000	5	0.993	(0;0.0037)	(0;0.0053)	0
	1,000	5	0.993	(0.0016;0.0116)	(0.0011;0.0141)	5
	10,000	50	0.99999	(0;0.0004)	(0;0.0005)	0
	10,000	50	0.99999	(0.0016;0.0037)	(0.0014;0.0041)	25
	10,000	50	0.99999	(0.0037;0.0066)	(0.0034;0.0071)	50

Absence of proof is not proof of absence

Table 2 and table 3 provide exact confidence intervals (CIs) on the true incidence (P = 0.001 or 0.005) of a rare serious adverse event (SAE) under various scenarios. In those tables, n = number treated, nP = expected number of SAEs, P(X \geq 1) = Probability of at least 1 SAE among n patients; Outcome = probable number of SAEs among n patients.

Early on in the monitoring for adverse events (AE's) of a newly approved drug, it is unlikely to have even 1 report of a rare serious adverse event (SAE). For example out of the first 150 patients exposed to the drug, the probability of observing no patient with an adverse event given that the true incidence in the population is 0.1% is 0.861. It is therefore likely that among 150 patients treated with the drug, there is an observed incidence of 0% (0/150). An exact 95% confidence interval [7] based on the 0/150 data ranges from 0% to 2.43% (Table 2 and Table 3). If what was known about the mechanism of action, the pharmacology and/or toxicology of the drug suggested certain untoward adverse events were possible, and one monitored specifically for such events, the fact that no such events were observed among 150 treated patients does not mean that the true incidence of such events is 0 – since the upper limit of the 95% confidence interval is 2.4%. As Dr. Paul Leber (former head of the CNS medical Review Division at FDA) often said “Absence of proof is not proof of absence”.

Monitoring adverse event rates as data accumulates

Table 1 illustrates how many patients would need to be treated before one has high confidence of seeing at least one rare AE. Table 2 and table 3 illustrate that zero occurrences of an AE of interest from patients treated in the post marketing life of a compound does not allow one to conclude that the incidence of that AE is zero. For example, from table 3, 0 SAEs among 1,000 patients treated is consistent with the true SAE rate being as high as 0.37% with 95% confidence and as high as 0.53% with 99% confidence.

Procedures exist that permit formal sequential, statistical monitoring of AE's of a drug in post-marketing as data accumulate (spontaneous reports). The methods of Schultz et al. [8], Fleming [9,10], Coe and Tamhane [11] or Peace [12,13] or Jennison and Turnbull [14] may be adapted for monitoring post-marketing AE's.

There are challenges in doing this: (1) the referenced procedures were developed for group sequential monitoring given a fixed, specified total number of patients to be treated. The analyses are to be conducted at each of a fixed number of stages, where the number of patients accrued between stages is usually taken to be the total number of patients to be treated divided by the number of analysis stages. Clearly in monitoring post-marketing AE's the number of patients to be treated is not known nor is it fixed. However, for monitoring purposes, one could develop a statistical monitoring plan based on a targeted number of patients to be treated within specified intervals of time. The intervals may be more frequent in the first year of post-marketing say, than in subsequent years. (2) Other challenges are what are the numerator and denominator of the incidence estimate at any particular point in time? This will require the company to use its own spontaneous reporting system as well as the FDA adverse event reporting system (FAERS).

Summary

This commentary has provided information to those developing monitoring plans for SAE's following regulatory approval of a new drug. In addition, we have (1) illustrated how many patients would need to be treated in order to have high confidence of seeing at least 1 pre-specified SAE, (2) shown that absence of proof of a SAE is not proof of absence of that SAE, and (3) identified methodology that could be used for formal statistical monitoring.

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