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WHITE PAPER

Adverse Event Estimation in Post Marketing

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Introduction

Sample size estimation is a mandatory exercise before undertaking any scientific study. This will help the researcher to plan and execute the study properly. However, the entire process depends up on the number of patients to be recruited for the proposed study. Hence the utmost care should be taken while calculating the sample size. The purpose of this paper is to provide a reference table containing sample size required for a post marketing clinical trial when there is no background incidence of adverse event in the general population. The table provides the sample size for various options such as the expected incidence rate of adverse reactions and the number of occurrence of a particular adverse reaction along with various statistical powers. A few examples are also provided in the paper for better understanding.

Sample size Estimation when there is no background incidence of Adverse Events

Suppose the expected incidence rate of adverse reactions is λ, the expected number of occurrences of a particular adverse reaction is a and the number of patients required to be studied is N. This N needs to be estimated. If the incidence of adverse reactions is reasonably low then one might assume that it follow a Poisson distribution. With these assumptions and for a given statistical power (1-ß), N satisfies the following equation.

$$\sum_{x=0}^{a-1} \frac{(N\lambda)^x e^{-N\lambda}}{x!} = ß$$

When **a** = 1 (i.e., when adverse reaction expected to occur only in one patient) then the above equation simplifies to

$$N = \frac{-\log ß}{\lambda}$$

For **a** > 1 there is no simple expression for the solution for the above equation but the same can be solved by using simulation methods. Thus the required sample size could be estimated from the above equations.

The following table gives required sample size for various options such as expected incidence rate of adverse reactions (λ), the number of occurrence of a particular adverse reaction (**a**) and statistical power (1-ß). This would be useful for future researchers as a ready reckoner.

Table 1: Sample sizes required to observe a total of a adverse reactions with a given probability 1-ß and anticipated incidence λ.

λ	a	Statistical power					
		50%	**60%**	**70%**	**80%**	**90%**	**95%**
0.0001	**1**	6932	9163	12040	16095	23026	29958
	2	16784	20224	24393	29944	38898	47439
	3	26741	31054	36156	42791	53224	62958
	4	36721	41753	47623	55151	66808	77537
	5	46710	52367	58904	67210	79936	91536
	6	56702	62920	70056	79060	92747	105131
	7	66697	73427	81111	90754	105321	118424
	8	76693	83898	92090	102326	117710	131482
	9	86690	94340	103007	113798	129948	144347
	10	96688	104757	113873	125188	142060	157053

0.0005	1	1387	1833	2408	3219	4606	5992
	2	3357	4045	4879	5989	7780	9488
	3	5349	6211	7232	8559	10645	12592
	4	7345	8351	9525	11031	13362	15508
	5	9342	10474	11781	13442	15988	18308
	6	11341	12584	14012	15812	18550	21027
	7	13340	14686	16223	18151	21065	23685
	8	15339	16780	18418	20466	23542	26297
	9	17338	18868	20602	22760	25990	28870
	10	19338	20952	22775	25038	28412	31411
0.001	1	694	917	1204	1610	2303	2996
	2	1679	2023	2440	2995	3890	4744
	3	2675	3106	3616	4280	5323	6296
	4	3673	4176	4763	5516	6681	7754
	5	4671	5237	5891	6721	7994	9154
	6	5671	6292	7006	7906	9275	10514
	7	6670	7343	8112	9076	10533	11843
	8	7670	8390	9209	10233	11771	13149
	9	8669	9434	10301	11380	12995	14435
	10	9669	10476	11388	12519	14206	15706
0.005	1	139	184	241	322	461	600
	2	336	405	488	599	778	949
	3	535	622	724	856	1065	1260
	4	735	836	953	1104	1337	1551
	5	935	1048	1179	1345	1599	1831
	6	1135	1259	1402	1582	1855	2103
	7	1334	1469	1623	1816	2107	2369
	8	1534	1678	1842	2047	2355	2630
	9	1734	1887	2061	2276	2599	2887
	10	1934	2096	2278	2504	2842	3142
0.01	1	70	92	121	161	231	300
	2	168	203	244	300	389	475
	3	268	311	362	428	533	630
	4	368	418	477	552	669	776
	5	468	524	590	673	800	916
	6	568	630	701	791	928	1052
	7	667	735	812	908	1054	1185
	8	767	839	921	1024	1178	1315
	9	867	944	1031	1138	1300	1444
	10	967	1048	1139	1252	1421	1571

Example 1

In a previous study, it was found that an anti-hypertensive drug produced cardiac arrhythmias in about 1 in 10,000 patients. A researcher decides that if drug under PMS study produces 3 such arrhythmias then the drug will have to be withdrawn from the market. He wishes to detect 3 events with a statistical power of 90%.

Solution:

In this given situation, we have the inputs such as 1 - = 0.90, incidence rate = 1/10000 = 0.0001 and a = 3. Then from the above table, the required sample size would be 53224 patients for the proposed study.

Example 2

In a previous study, an anti-diabetic drug produced a particular adverse event in about one in 100 patients. A researcher decides that if a new anti-diabetic drug produces two such adverse events then the drug will have to be withdrawn. He wishes to detect two events with a statistical power of 80%.

Solution:

In this situation, we have the inputs such as statistical power 1 - = 0.80, expected incidence rate = 1/100 = 0.01 and the anticipated occurrence of the adverse events a = 2. Then from the above table, the required sample size would be N = 300 patients for the proposed study.

Conclusion

The sample size estimation is an important step in the planning of a post marketing clinical trial especially when there is no background incidence of adverse events in the general population. The table provided above would certainly help the researcher to avoid the cumbersome mathematical calculations to estimate the sample size for the proposed study. Thus the table could be used as a ready reckoner for any post marketing clinical research to estimate the adverse events.

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Reference:

1.David Machin, Michael J. Campbell, Say Beng Tan, Sze Huey Tan. Sample Size Tables for Clinical Studies: Wiley-Blackwell; 2009.