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RASOR RESOURCE NEWSLETTER
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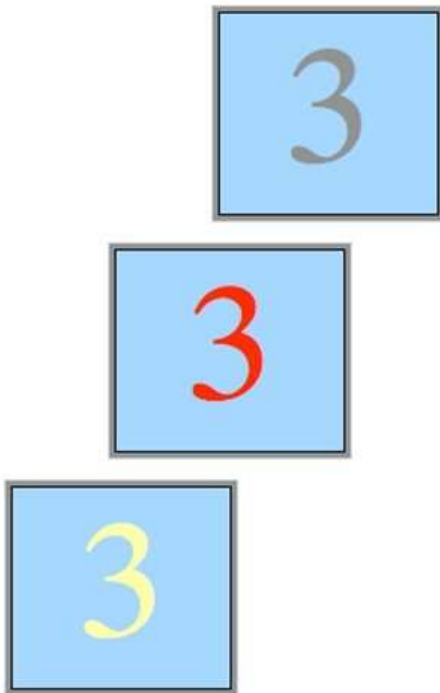
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Greetings Julia:

We thank our readers for the fabulous response to our last newsletter where we shared the sample size needed to discover most or all of the usability problems with a particular medical device. In this issue, we will demonstrate the value and use of the Rule of Three in clinical trial sample size determination when evaluating the safety of a medical device and, for those interested, how the number 3 is curiously related to many aspects of life. I hope you find the resources in our newsletter as useful as my clients and I have.

Julia S. Razor
 Medical Device Strategist

Resource



(N) Number of Subjects Needed for a 95% Certainty of Observing at Least One Subject with an AE Rate Equal to R	(R) Adverse Event (AE) Rate in a Population	(NR) Number of Subjects Times the Adverse Event Rate
25	12.0%	3
50	6.0%	3
75	4.0%	3
100	3.0%	3
125	2.4%	3
150	2.0%	3
175	1.7%	3
200	1.5%	3
300	1.0%	3
400	0.8%	3
500	0.6%	3
600	0.5%	3
700	0.4%	3
800	0.4%	3
900	0.3%	3
1000	0.3%	3
1100	0.3%	3
1200	0.3%	3
1300	0.2%	3
1400	0.2%	3
1500	0.2%	3

NOTE: N=3/R; R=3/N; N*R=3 (The Rule of 3)

Topic: Value of the "Rule of Three" in Clinical Trial Sample Size Determination when Evaluating Device Safety

Rule of Three: If you observe n patients, and none of these patients have an adverse event, then a 95% confidence interval for the probability of an adverse event goes from zero to $3/n$ [<http://www.childrensmercy.org/stats/size/zeroevents.asp>]. This Rule of Three of seemingly unknown origin was first discussed in medical literature in 1983 [<http://www.jstor.org/pss/2685405>, Hanley, Lippman-Hand. JAMA 249(13): 1743-45, 1983.]

Problem: How many subjects (sample size) are needed to evaluate the safety of a medical device in a clinical trial? OR: FDA requires enough subjects to test for rare adverse events (AEs) that occur at a rate of at least 1%; what method could be used to determine sample size?

Solution: Below, Eugene R. Heyman, PhD explains how to use the Rule of 3 to determine the sample size needed. Refer to the table above for the following discussion.

"To be 95% certain of observing at least one patient with an adverse event, the expected value of the AE must be 3. The expected value is the total number of patients times the rate of the AE in the population. For example, if the sample size is 200 and the rate of a specific AE is 1.5% then $200 \times 0.015 = 3$. So, divide 3 by your sample size to obtain the necessary rate. Take a sample size of 150. $3/150 = 0.02$. This means that with a sample size of 150 you are 95% certain to observe at least one patient with a particular AE if the true rate of the AE in the population is 2%. As you see, as the sample size increases you are more likely to observe at least one patient with rarer AEs. To look at it the other way, let's assume you want to be 95% certain to detect an AE with a rate of 1%. You divide 3 by the AE rate to obtain the necessary sample size. $3/0.01 = 300$ patients necessary to be 95% certain of observing at least one patient with an AE with a rate of 1%. This is (believe it or not) called the rule of 3."

Eugene R. Heyman, PhD points out: To be 95% certain to detect an AE with a rate of 1%, you divide 3 by the AE rate to obtain the necessary sample size: $3/0.01 = 300$ patients. This is (believe it or not) called the Rule of 3.

Many times when testing a new device for *efficacy*, a statistically significant difference from the control device can be demonstrated in a clinical trial with far fewer subjects than 300. However, to test device *safety* for the occurrence of rare adverse events, a larger sample size is needed. Generally, a larger sample size is seen in trials for Class III devices considered to have a significant safety risk, e.g., combination products or implantables. These devices are associated rare adverse events that are serious in nature and they usually require clearance via PMA. A smaller sample size is typical for Class II devices with less serious risks and they usually require clearance via the 510(k) path.

Acknowledgement: Many thanks to my colleague who shared this Resource and gave his permission to quote his explanation in this issue of Razor Resource: Eugene R. Heyman, PhD, Statistical Consulting, Montgomery Village, MD.

For Those Interested: To read about how the number 3 is curiously related to many other aspects of life, go to [http://en.wikipedia.org/wiki/3_\(number\)](http://en.wikipedia.org/wiki/3_(number)).

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