

MEMORANDUM FOR WILLIAM NOE,
ELECTRICAL ENGINEER

May 31, 2001

FROM: John M. Dawson

SUBJECT: Model 3100 High Frequency Oscillatory Ventilator: Addition of Model 3100B to Models 3100 and 3100A Product Family, by SensorMedics, P890057/S14/A1, March 30, 2001

This submission amends supplement 14 of the Multicenter Oscillator ARDS Trial (MOAT2) – ARDS means Acute Respiratory Distress Syndrome – which was originally authorized by G960017. Some 148 patients were randomized 1:1 to the experimental High Frequency Oscillatory Ventilator (HFOV) and Conventional Mechanical Ventilation (CMV), and tested for device success and adverse events at 30 days and 6 months. My review is of the study protocol at pages 105-141, the clinical report, and the statistical review memos by Judy Chen of G960017 of 2/26/96 and 6/24/96. The sponsor met the sample size indicated in the protocol, and did the promised calculations.

Quoting from p.164: “The primary study hypothesis was that death or continued respiratory support at 30 days would, with 95% confidence, be not worse than 10 points in the HFOV group as compared to the CMV group.” – i.e. a non-inferiority alternative hypothesis, to be tested against a null hypothesis of HFOV worse than CMV by more than 10 points.

1. Death or continued therapy at 30 days. Sponsor states on p.164 that the primary endpoint, rate of death or continued therapy (“failure”) “was not met”. In Table 7 on p.164 they cite failure rates of 79% for HFOV and 74% for CMV, with a difference of $79\% - 74\% = 5\%$, with a 95% confidence interval on the difference extending from -10% to $+20\%$. My results agree with sponsors, given in Appendix 1 below. The fact that the confidence interval on the difference extends above 10% - in fact, to 20% - means that the null hypothesis of HFOV rate inferiority cannot be rejected.

2. Mortality within 30 days. Sponsor had no study hypothesis relating to mortality alone, but on p.163 concluded that “The data suggests that HFOV patients were less likely to exit as a result of death” The results in Table 7 on p.164 indicate 37% mortality for HFOV versus 52% for CMV, within 30 days, an apparent advantage for HFOV. The 95% confidence interval on the difference overlaps zero, however, as shown in Table 7, and on which I concur in Appendix 2 below. This overlapping of zero means that zero cannot be excluded as a plausible true difference in mortality rates, and contradicts sponsor’s “less likely to exit as a result of death” statement. This result does not support a claim of better mortality experience for HFOV.

3. Weaning from mechanical ventilation. Sponsor’s statement on p.163 includes this: “The data suggests that HFOV patients were ... more likely to exit after being weaned

from mechanical ventilation.” As with mortality, there was no study hypothesis for weaning itself. Their Table 6 on p.163 cites 37% HFOV patients weaned, versus 27% for CMV. They don’t offer any confidence interval analysis of the apparent advantage for HFOV, but my calculations in Appendix 3 below show 95% confidence limits overlapping zero. As with mortality, the overlapping of zero means zero is a plausible true value for the difference in weaning outcomes.

Effect of sample size? Though the sample size goal set in the IDE was achieved in the MOAT2 study, it was modest. The usual penalty for small sample size is that it tends to frustrate a sponsor’s hope to achieve tight confidence intervals on differences between treatment and control performance measures. One convenient way to evaluate sensitivity of results to sample size is to, say, double the samples size, while holding the treatment and control point estimates (percentages) as observed. The one difference is in the case of mortality: at the hypothetical doubling of the sample size, the 52% versus 37% excess in CMV mortality would have a confidence interval that excludes zero – i.e. at twice the sample size, the apparent difference would be statistically significant. In the case of the failure and weaning rates, however, statistical significance does not emerge from a doubling of sample size.

Other concerns:

4. Poolability. The survival percentages need to be presented for the 9 participating sites that had both HFOV and CMV patients, to justify relying on the pooled results on pages 163-165. I should note that poolability appears not to have been addressed in the IDE stage. It depends on a showing of homogeneity of performance, which in this case might be satisfied by showing that the 30-day rate is consistently higher for HFOV than CMV.

5. Crossovers. The protocol says at p.5 and 6 of 37 that MOAT2 would not be a crossover study, but allowed for treating physicians to “be offered the conventional therapy, if in the opinion of the physicians, they would benefit from it.” Judy’s 2/26/96 memo cautioned sponsor to keep detailed records of any crossovers. Leaving use or non-use of either device, or both, to the discretion of the treating physician potentially makes the study an *observational* study rather than a *controlled* study – i.e. compromises scientific quality. Sponsor should account for the experience and baseline characteristics for those patients who did, and did not, cross over – e.g. the 30-day survival percentages for the groups separately. My question would be whether if the physician chose to add CMV to HFOV, would that not constitute a *failure* of HFOV for that patient?

CONCLUSION. None of the confidence interval analyses above are favorable to sponsor, on the failure, mortality or weaning variables. It is arguable that the comparison of HFOV and CMV mortality rates might have favored HFOV statistically, if the sample size had been twice what it was, but that hypothetical doubling would not help the primary failure endpoint, nor weaning from mechanical ventilation. I am concerned about sponsor’s omission of justification for pooling across sites, and about the possible impact of the crossing over of HFOV patients to CMV on the definition of treatment failure.

Appendix 1. – Comparison of HFOV and CMV 30-day failure rates

The output shows that I asked for 90% CI, which was the way of getting a 1-sided higher 95% CL.

StatXact-4 Output

Date: Thursday, May 31, 2001

DIFFERENCE OF TWO BINOMIAL PROPORTIONS

Statistic based on the observed 2 by 2 table :

Binomial proportion for column <col1 > : pi_1 = 0.7397 ← CMV
Binomial proportion for column <col2 > : pi_2 = 0.7867 ← HFOV
Difference of binomial proportions : Delta = pi_2 - pi_1 = 0.04694
Standardized difference of binomial proportions : Delta/Stdev = 0.6723

Results:

Method	P-value(2-sided)	95.00% Conf. Interval of Delta
Asymp	0.5014	(-0.08991, 0.1838)
Exact	0.5555	(-0.1107, 0.2208)

Elapsed time is 0:0:3.10

The observed table:

	CMV	HFOV
Failures	54 (73.97 %)	59 (78.67 %)
Successes	19 (26.03 %)	16 (21.33 %)

Appendix 2. – Comparison of HFOV and CMV 30-day mortality rates

StatXact-4 Output

Date: Thursday, May 31, 2001

DIFFERENCE OF TWO BINOMIAL PROPORTIONS

Statistic based on the observed 2 by 2 table :

Binomial proportion for column <col1 > : pi_1 = 0.3733 ← HFOV
Binomial proportion for column <col2 > : pi_2 = 0.5205 ← CMV

Difference of binomial proportions : $\Delta = \pi_2 - \pi_1 = 0.1472$
 Standardized difference of binomial proportions : $\Delta/\text{Stdev} = 1.821$

Results:

Method	P-value(2-sided)	95.00% Conf. Interval of Delta
Asymp	0.0687	(-0.01127, 0.3057)
Exact	0.0842	(-0.01969, 0.3180)

The observed table:

	HFOV	CMV
Died	28 (37.33 %)	38 (52.05 %)
Survived	47 (62.67 %)	35 (47.95 %)
Total	75	73

Appendix 3. – Comparison of HFOV and CMV percents weaned from mechanical ventilation

StatXact-4 Output

Date: Thursday, May 31, 2001

DIFFERENCE OF TWO BINOMIAL PROPORTIONS

Statistic based on the observed 2 by 2 table :

Binomial proportion for column <col1 > : $\pi_1 = 0.3733 \leftarrow$ HFOV
 Binomial proportion for column <col2 > : $\pi_2 = 0.2740 \leftarrow$ CMV
 Difference of binomial proportions : $\Delta = \pi_2 - \pi_1 = -0.09936$
 Standardized difference of binomial proportions : $\Delta/\text{Stdev} = -1.300$

Results:

Method	P-value(2-sided)	95.00% Conf. Interval of Delta
Asymp	0.1937	(-0.2492, 0.05047)
Exact	0.2236	(-0.2733, 0.05828)

The observed table:

	HFOV	CMV
Weaned	28 (37.33 %)	20 (27.40 %)
Not Weaned	47 (62.67 %)	53 (72.60 %)
Total	75	73