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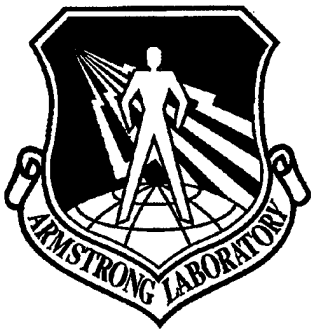

ARMSTRONG LABORATORY

RESEARCH PROTOCOL FOR THE EVALUATION OF MEDICAL WAIVER REQUIREMENTS FOR THE USE OF LISINOPRIL IN USAF AIRCREW - INTERIM REPORT, SUMMER 1995

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November 1995

Interim Technical Report for Period February 1994 – March 1995

AIR FORCE MATERIEL COMMAND
BROOKS AIR FORCE BASE, TEXAS

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The Office of Public Affairs has reviewed this technical report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This technical report has been reviewed and is approved for publication.

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REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 1995	Interim–February 1994–March 95

4. TITLE AND SUBTITLE
Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew - Interim Report, Summer 1995

5. FUNDING NUMBERS
PE – 62202F
PR – 7755
TA – 27
WU – 23

6. AUTHOR(S)
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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
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8. PERFORMING ORGANIZATION REPORT NUMBER
AL/AO-TR-1995-0116

9. SPONSORING/MONITORING AGENCY NAMES(S) AND ADDRESS(ES)

10. SPONSORING/MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 words)

This is the first annual report on the Lisinopril Study Group recruited under the Research Protocol for the Use of Lisinopril in USAF Aircrew. Our objective was to measure progress toward the goals of determining the degree to which aviators on lisinopril require individual centralized evaluation and the degree to which clinical criteria can be identified for the establishment of medical waiver evaluations by local Flight Surgeons. Our analysis consisted of examining the data collection process as implemented through the Research Protocol and examining the data collected to date in terms of trends and requirements relative to the statistical hypotheses set forth in the Protocol. Examination of the data collections process resulted in two measures: changing the Research Protocol to reflect the current USAF G tolerance Training Standard of 7.5 G for 15 seconds in an upright seat and incorporation of a specific data collection form for the Lisinopril Study Group's G Tolerance Protocol. From our data analysis, we conclude that current trends in the waiver rate and the clinical and G tolerance data indicate that continuation of the study is justified and likely to result in definitive conclusions regarding the Research Hypotheses. The study is on schedule in terms of recruitment rate is yielding useful information. No other changes are suggested.

14. SUBJECT TERMS
Hypertension
Lisinopril
USAF Aircrew Medical Standards

15. NUMBER OF PAGES
52

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

CONTENTS

1. Objectives

The *Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew* [1] (hereafter referred to as the "*Research Protocol*") is dated February 11, 1994. As described in the *Research Protocol*'s Experimental Plan, the study is intended to be carried out over five years, with the data analyzed semi-annually the first year and annually thereafter.

A semiannual analysis of the progress of the study group with respect to disqualifying conditions was performed, informally, in September, 1994. At that time, there had been no disqualifying conditions attributed to the use of lisinopril by a study group member, and there was clearly an insufficient number of high-performance aircrew in the study group to justify an in-depth analysis of centrifuge data. For these reasons, a more extensive interim analysis was not deemed to be appropriate at that time.

The present report documents the first annual interim analysis of the *Research Protocol* (included as Appendix C to this report). The general objective of an interim analysis is to determine the progress being made toward fulfilling the objectives of the study under question. Thus, the overall objective of this interim report is to document the progress made during the first year toward fulfilling the objectives of the *Research Protocol* for the Lisinopril Study Group.

An interim analysis is traditionally understood as consisting of:

1. monitoring the progress of the study with respect to the projected timetable and with respect to adherence to the protocol, and

2. analyzing the data collected up to the point of the interim observation, with a view toward detecting statistically significant trends in the data, and, in particular, with a view toward detecting trends that would justify stopping the study.

These general objectives are addressed in the *Research Protocol* in terms of particular points involving recruitment rates and stopping criteria. The stated purposes of the interim analyses, as given in the *Research Protocol* are:

1. to determine approximately how many subjects will be required to adequately test the Research Hypothesis, and

2. if given the current rate of subject recruitment and follow-up, whether that number will be reached within the planned five-year duration of the study.

Furthermore, it is stated that the study is to be terminated when:

1. the number of subjects required for adequate testing is reached, or

2. if in the opinion of the investigators, it is obvious that the Research Hypothesis cannot be supported by the data.

Here, the term "Research Hypothesis" is to be identified with "the hypothesis stated in Section 6" of the *Research Protocol*, which is given in the form of the following objective:

> To determine if aviators on lisinopril for the treatment of primary hypertension require individual centralized evaluation at the Aeromedical Consultation Service or can clinical criteria be identified to establish Local Flight Surgeon's Office medical waiver evaluations.

Thus, the objectives of the interim analysis consist of systematically considering the objectives of the *Research Protocol* itself in light of the status of the study at the time of the interim observation.

The detailed expression of the above stated Research Hypothesis in terms of specific research questions is given in the *Research Protocol* (Appendix C). The corresponding evaluation protocols and statistical methodologies are described in Section 2 of this interim report. Section 3 of this interim report presents details of the progress made, through March 6, 1995, toward reaching the objectives of the *Research Protocol.* We conclude in Section 4 with a discussion of the results of this interim review.

2. Methods

In pursuit of the objectives described above, we review the evaluation methodology by which the Study Group data is collected and then proceed to describe the analysis methodology.

2.1 Evaluation Methodology

The *Research Protocol* specifies a comprehensive clinical evaluation for all Study Group members, which includes a G-tolerance evaluation for all members who serve as crew members in high-performance aircraft and would otherwise be considered waiverable under the clinical evaluation plan. We shall briefly review these protocols. A more detailed discussion can be found in the *Research Protocol* [1].

2.1.1 Clinical Evaluation Protocol

The Clinical Evaluation Protocol for the Lisinopril Study Group consists of the standard Aeromedical evaluation for disqualifying medical conditions, augmented with special attention to detection of possible aeromedically significant side effects of Lisinopril. Quoting from the *Research Protocol*, the evaluation consists of the following:

1. Flight medicine evaluations, including medical history, with a review of outpatient record, a review of systems, and a physical exam;

2. Daily indirect, seated, blood pressure reading;

3. ACS clinical pathology laboratory screen to include CBC (complete blood count) with differential, platelet count, fasting glucose, potassium, calcium, creatinine, uric acid, total cholesterol, HDL (high density lipoprotein) cholesterol, triglyceride, total bilirubin, SGPT (serum glutamic-pyruvic transaminase), SGOT (serum glutamic-oxaloacetic transaminase), alkaline phosphatase, GGT (γ-glutamyl transpeptidase), sedimentation rate, BUN (blood urea nitrogen), and a routine urinalysis;

4. Diagnostic radiology, including PA and lateral chest x-rays, on all evaluees, and a cardiac flouroscopy if male evaluee's age is >35 years (cardiac flouroscopy would not be accomplished on female aviators);

5. Audiology, including pure-tone audiometry and tympanometry;

6. An oculovestibular evaluation, including harmonic oscillation, optokinetic test, smooth pursuit and saccadic tracking;

7. Opthalmologic exam, including cycloplegic refraction, intraocular tonometry, slit lamp exam, visual fields by confrontation, stereopsis, color perception, ocular motility, and contrast sensitivity;

8. Symptom-limited treadmill exercise tolerance test, echocardiography, 24-hr. ambulatory ECG (electrocardiogram) monitoring, and pulmonary function tests.

2.1.2 G Tolerance Testing Protocol

The Lisinopril Study Group G Tolerance Protocol consists of the following two centrifuge protocols.

Standard Medical Evaluation G Profiles

1. **GOR 1:** Gradual onset (0.1 G/sec) run, with evaluee relaxed, and terminating with the visual end-point.

2. **RORs:** Rapid onset (6 G/sec) run series, with evaluee relaxed, lasting 15 seconds at $2.8 + 0.3 \times n$ G, for n=0,1,2,3,... , or terminating with the visual endpoint.

3. **GOR 2:** Gradual onset (0.1 G/sec) run, with evaluee relaxed, and terminating with the visual end-point.

4. **GORS:** Gradual onset (0.1 G/sec) run, with evaluee performing an L-1 anti-G straining maneuver, and terminating with the visual end-point.

Failure to complete the 3.1 G ROR is considered an indication of low G tolerance.

Standard Training G Profiles

This is a series of rapid onset (6 G/sec) runs with straining. The runs are accomplished with the evaluee wearing a functioning anti-G suit and performing an anti-G straining maneuver and are terminated with the visual end-point or loss of consciousness. The test consists of an 8 G, 15 second G tolerance standard run, preceded by three practice runs. The G tolerance standard run may be repeated up to two times in pursuit of the standard. The series profiles are:

1. A 3 G, 15 second, warm-up run.

2. A 5 G, 30 second run for practicing the ant-G straining maneuver.

3. A 7 G, 15 second practice run (optional).

4. One to three 7.5* G, 15 second training goal / G tolerance standard runs.

Evaluees who cannot complete the 7.5 G, 15 second Standard Training Profile exposure without losing consciousness or reaching the visual end-point are considered to have low G tolerance.

The evaluee will have up to three attempts to accomplish this standard. If after three attempts the evaluee is still unable to perform to the level of the standard, only a categorical (non-high performance) waiver can be considered.

* The protocol was written with 8 G as the standard, but the current Air Force Aircrew standard has been decreased to 7.5 G.

2.2 Analysis Methodology

In the *Research Protocol* [1], it is proposed that the research hypotheses be examined by addressing three questions through statistical analysis. The answers to these questions are to form the basis for determining the continuation of all or part of the study. These questions are:

1. Is the overall yield of waiverable aviators among the study subjects below 50%?

2. For any particular cluster of tests (G tolerance, coronary artery disease, etc.), is the prevalence of a disqualifying condition greater than or less than 5%?

3. For any test that yields a continuous response, is the mean value for Lisinopril subjects different from the mean of aeromedically "normal" subjects?

Our statistical analysis methodology at the interim analyses and the in the final analysis is centered around the statistical formulation of these questions. Since they all involve comparison of Study Group outcomes to various standards, we shall describe in turn our choice of standards and the general form of the comparisons.

2.2.1 Control Standards

The overall yield of waiverable evaluees among the Study Group members is to be compared against 50%. The rationale for this standard considers that if Aviators are waivered at a proportion of less than 50%, then it may not be efficient to continue the study.

For each cluster of tests in the Clinical Evaluation Protocol and in the G Tolerance Protocol, the prevalence of disqualifying conditions attributable as a side effect of lisinopril shall be compared against 95%. The rationale for this standard percentage considers that aeromedically significant side effects are not conducive to "safety of flight" and therefore the medication may not be useful for the treatment of aviators with hypertension.

On the other hand, the G tolerance results for the Medical Evaluation Profile are continuous variables and can thus be compared against an existing control group in terms of measures of central tendencies. There are two published studies containing control group data based on the same Medical Evaluation Profile as specified for use for the Lisinopril Study Group. The data is specified in the following table,

Group	GOR 1	ROR-Pass	GOR 2	GORS
Women's G Study (Males)[1]	4.79±0.75 (139)	3.35±0.49 (125)	4.52±0.72 (129)	5.67±0.81 (114)
MVP Control Group[2]	4.65±0.8 (434)	3.34±0.5 (~434)	4.45±0.7 (~434)	5.56±0.9 (~434)

where the superscripts correspond to the following publications:

1. Gillingham, et al., 1986 [2]. (GOR onset rate: 0.067 G/sec., ROR onset rate: 1 G/sec.)

2. Whinnery, 1986 [3]. (GOR onset rate: 0.067 G/sec., ROR onset rate: 1 G/sec.)

Our first inclination was to use the larger group, which is the MVP Control Group. On the other hand, the centrifuge evaluation criteria given in the Lisinopril Protocol (see section 2.1.1 above) quotes GOR 1 and GOR 2 means and standard deviations for "medical evaluees" without specific reference to published literature, but which correspond closely to the figures reported in the Women's G Study paper.

We finally chose the larger MVP Control Group as our retrospective control group, because of sample size considerations and the fact that the reasons that led to a different control group being selected for the Women's G Tolerance Study do not apply in the present case. (The main reasons given in the Women's G Tolerance paper are a desire for more uniform exposure and a desire to select novices to centrifuge exposure.)

Extracting the Medical Evaluation Profile for the control group in the MVP paper, we have:

Profile	N	Mean	Standard Deviation
GOR 1	434	4.65	0.8
ROR - pass	434	3.34	0.5
GOR 2	434	4.45	0.7
GORS	434	5.56	0.9

where "ROR-pass" refers to the highest ROR G level for which the evaluee completed the full 15 seconds.

We shall take this as our Control Data, and Gillingham, et al., 1986 [2], as our chief reference in interpreting the G tolerance results.

Since Dr. Gillingham wrote the centrifuge protocol for the Lisinopril *Research Protocol*, we feel comfortable in viewing the types of G tolerance comparisons made in the 1986 paper as our de facto standard for comparing the Lisinopril Study Group to this Control Data.

2.2.2 Statistical Methods

The comparisons we shall be making are of two types. First, we shall be comparing the proportions of waiverable aviators and disqualifying conditions in the Lisinopril Study Group to fixed standards, and, secondly, we shall be comparing the means of the G tolerance test results for the Lisinopril Study Group and the Control Group.

Since our interest is solely in detecting decreased compliance with aeromedical standards in the Lisinopril Study Group, we shall focus on one-sided tests of the form:

Null Hypothesis, H_0: $\theta_{lisinopril} < \theta_{standard}$,

Alternative (Research) Hypothesis, H_a: $\theta_{lisinopril} \geq \theta_{standard}$,

where θ represents the population parameter under consideration. If our sample statistics indicate that the reverse case is likely, we would perform tests with the forms of the hypotheses interchanged.

Thus, for testing proportions, we shall perform one-sided tests of the binomial proportion versus the appropriate standard, and for the comparisons of means, we shall perform one-sided, unpaired t-tests. Since standard chi-square tests of the binomial proportion depend upon sufficient sample sizes for application of the central limit theorem, we shall compare our sample size against conventional criteria and use exact computations if appropriate. Likewise, since the standard t-test assumes a normal distribution with equal variance for both the Study Group and the Control Group, we shall perform tests for normality and equality of variances, and make adjustments in our methodology as required. Confidence intervals will also be computed.

Our working methodology for this first interim analysis is to perform significance tests where the sample size is adequate. If these results meet conventionally significance criteria (probability of Type I error of no more than 5%), then we shall consider the stopping criteria met for the particular protocol element and consider whether termination of the element should be recommended. If this does not occur, we shall project sample size and/or power requirements for testing at future interim analyses.

3. Results: Interim Monitoring and Data Analysis

We shall discuss, in turn, interim results relevant to the three statistical questions posed above.

3.1 Yield of Waiverable Aviators

As of March 6, 1995, there were 40 aviators enrolled in the Lisinopril Study Group. Of these, 34 were recommended for waiver by the Aeromedical Consultation Service.

In examining the overall rate of waivers given to aviators in the Study Group, we shall test the proportion of evaluees waivered against a standard of 50%.

Using 50% as our test standard ($p_0 = 0.50$), the sample size of $n = 40$ meets the criteria, $n \cdot p_0 \cdot (1-p_0) \geq 5$, given in Woolson [4] for application of the normal or chi-square tests. On the other hand, we shall be using the binomial distribution directly in the following sections, so we also use it here for the sake of consistency. Thus, we performed a one-sided significance test of

$$H_0: p_{lisinopril} < p_0 \quad \text{vs.} \quad H_a: p_{lisinopril} \geq p_0,$$

for $p_0 = 0.50$, using the exact binomial distribution with the number of trials equaling 40.

The exact p-value for 34 waivers (5 disqualifications and 1 "no recommendation") out of 40 tests is 0.0000041823 and the 95% lower confidence limit on the proportion of successes for the Lisinopril Study Group is 0.72525, or about 72.5%.

Summarizing, we have

	P-Value for Rejecting $H_0: p_{lisinopril} < p_0$	95% Lower Confidence Interval on the Proportion of Waivers
Overall Rate of Waivers	0.000004	0.725

Thus, we already have considerable evidence that the overall rate of waivers among Lisinopril Study Group members is much greater than 50%.

3.2 Clinical Evaluation Test Clusters

For each cluster of tests in the Clinical Evaluation Protocol , we are interested in comparing the prevalence of disqualifying conditions attributable to side effects of lisinopril against a standard of 95%.

As of March 6, 1995, there have been no reports or observations of aeromedically significant side effects of lisinopril among Study Group members relative to any of the Clinical Evaluation Protocol test clusters.

For the interim sample size of n = 40, and comparing against the standard of 95% ($p_0 = 0.95$), we cannot satisfy the criteria, $n \cdot p_0 \cdot (1-p_0) \geq 5$, given in Woolson [4] for application of the normal or chi-square tests. (In fact, we would need n=105 to satisfy this criteria.) On the other hand, if we wish to compute the exact binomial p-value we can determine through numerical trial-and-error that, in principle, we will require a sample size of at least n=56, with no aeromedically significant side effects, to achieve a statistically significant result ($p < 0.05$).

Thus, it is not meaningful, from a statistical point of view, to attempt to address trends in frequencies of clinical test outcomes at this time.

3.3 G Tolerance Protocol Test Cluster

In reviewing the results for the G Tolerance Protocol, it was apparent that there were deviations from the centrifuge profiles as specified in the *Research Protocol* [1]. Therefore, we shall present a more detailed examination of the G tolerance data, and then follow with an analysis.

3.3.1 G Tolerance Data Monitoring

As of March 6, 1995, there were 9 members of the Lisinopril Study Group who were currently serving in high-performance aircraft, and who were thus enrolled in the G Tolerance Protocol subgroup.

The Medical Evaluation Profile results are summarized in the following table, where the bracketed entries represent results from compromised protocol compliance and the averages are computed without these values included. The nature of the compromised protocol compliance for each case is given a more detailed presentation in the Appendix ("G Tolerance Evaluations") to this report.

Case Number	GOR 1	ROR - pass	GOR 2	GORS
1	4.0	2.8	3.9	6.7
2	6.3	[4.6]	[5.7]	[7.1]
3	3.6	3.1	3.6	5.4
4	8.4	[4.0]	-	[7.8]
5	4.5	3.1	4.8	7.2
6	6.4	[4.0]	[5.5]	[6.2]
7	6.06	-	-	[7.5]
8	6.0	-	-	-
9	5.6	-	-	[7.4]
Average	5.65 (9)	3.00 (3)	4.10 (3)	6.43 (3)

As is easily noted from the table, only 3 of the 9 subjects entered in the G tolerance subgroup to date were administered a testing protocol in complete compliance with that specified in the *Research Protocol.* The data for 3 subjects was compromised by using either the wrong onset rate or the wrong G-step increment in the ROR series. In addition, in one of these cases, the GOR 2 run was not performed. In addition, 3 of the subjects are missing ROR and GOR 2 data entirely.

For both of the evaluees given the wrong G-step increment, the GORS level was lower than the GOR 1 level , which is opposed to the pattern of response for all of the other evaluees. This would seem to call into question the value of all of the Medical Evaluation Profile measurements for these evaluees, with the exception of GOR 1. Generally, non-compliance with the protocol results in an altered pattern of physiological stress throughout the profile, and could result in a different pattern of response than would have been attained if the protocol had been followed.

The GOR 1 data is our only complete and uncompromised set of data for the 9 G tolerance subjects. Unfortunately, Gillingham [2] did not consider this run to be the most reliable component of the protocol due to possible psychological factors associated with the first run. This is the reason the second GOR run was added G tolerance evaluations by Dr. Gillingham.

It is our opinion that the ROR-pass data and the GOR 2 data are too incomplete, and should not be used as part of an interim statistical analysis. Furthermore, the GORS data, while being more complete, is

compromised by following the ROR and GOR 2 measurements in the protocol; therefore, we have also excluded it from the present interim analysis.

Although the Training Profile was administered correctly to only 4 of the 9 subjects, all 9 were rated by the centrifuge evaluator as qualified to high-performance aircraft, and will thus be counted as 9 qualifying evaluations.

3.3.2 G Tolerance Interim Analysis

Medical Evalutation Profile. Because of the problems just discussed, we based our interim Medical Evaluation Profile comparisons only on the GOR 1 data.

The data for the GOR 1 run are summarized in the following table.

	Sample Size	Mean	Standard Deviation
Lisinopril Study Group	9	5.65	1.46
Control Group	434	4.65	0.80

Since our intention was to apply one-sided, unpaired t-tests to the comparison problem, we decided to first test the assumptions that the two groups were drawn from normal populations with equal variances.

We tested the normality of the Lisinopril Study Group using the Shapiro-Wilk statistic as presented in the SAS System's UNIVARIATE procedure. There was insufficient evidence to reject the hypothesis that the population is normal ($p >> 0.05$). Normality of the Control Group was assumed.

Because of the apparent difference in sample standard deviation between the two groups, we performed an F-test for equality of variances to determine if the assumption of equal variances was statistically justified. Recall that in the F-test, we are testing H_0: $\sigma^2_{lisinopril} = \sigma^2_{control}$ vs. H_a: $\sigma^2_{lisinopril} \neq \sigma^2_{control}$. In the present case, we were using the F-test as a decision rule for choosing between types of t-test to apply in comparing the population means, so we adopted the convention that we would reject H_0 if the p-value for the test statistic was less that 0.05. The p-value for the GOR 1 data was approximately 0.001, so we proceeded under the assumption that the population variances were not equal.

We used the Satterthwaite t-test for unequal variances to compare the population means. As a consistency check, we also computed the corresponding Cochran-Cox t-test. We found the values to be virtually the same, so we have chosen to present the Satterthwaite test because it is computationally simpler. Since our sole interest is in determining whether the Lisinopril Study Group performs as well as the Control Group, we performed one-sided tests of H_0: $\mu_{lisinopril} < \mu_{control}$ vs. H_a: $\mu_{lisinopril} \geq \mu_{control}$, comparing the p-value of the test statistic against the conventional significance level of 0.05. For the GOR 1 data, we attained a p-value of approximately 0.037. Furthermore, we found the 95% lower confidence limit on the difference of means, $\mu_{lisinopril} - \mu_{control}$, to be approximately 0.0934.

Summarizing, we have

	P-Value for Rejecting H_0: $\mu_{lisinopril} < \mu_{control}$	95% Lower Confidence Interval on the Difference of Means $\mu_{lisinopril} - \mu_{control}$
GOR 1	0.037	0.0934

Training Profile. In examining the Training Profile, we are interested in testing the proportion of qualifying evaluees against 95%.

All 9 subjects in the G Tolerance Subgroup were classified as qualified to fly high-performance aircraft by the centrifuge evaluator after completing the Training Profile. As mentioned previously, the Training Profile was, in most cases, not carried out as specified in the *Research Protocol*; however, we feel that we have no choice except to accept the dichotomous decision of the evaluator as a basis for analysis.

Unfortunately, the situation here is the same as that for the Clinical Evaluation Protocol test clusters. With a sample size of n = 9, we cannot meaningfully compare against a standard of 95%. Again, to compute an exact binomial p-value, even with no disqualifications, we will require a sample size of at least n=56. Thus, it is not meaningful to attempt to address trends in frequencies of Training Profile outcomes at this time.

4. Discussion

In conclusion, we discuss the main issues arising from this interim observation of the Study Group.

4.1 Protocol Compliance

Review of the data as of March 6, 1995, reveals that the Clinical Evaluation Protocol is being followed well. This, of course, is not surprising since this part of the protocol basically corresponds to the standard examination and testing for all aviators referred to the Aeromedical Consultation Service.

On the other hand, compliance with the G Tolerance Protocol was much less consistent. This issue has been addressed by conferring with the centrifuge staff. As an aid to future compliance, evaluees referred from Aeromedical Consultation Service for centrifuge testing will have a special form (see Appendix B) attached as a cover sheet to their records which specifically delineates the structure and type of testing required by the *Research Protocol.*

As a result of conferring with the centrifuge staff, one change has been made to the G Tolerance Protocol. The training standard specified as 8 G in the Protocol has been changed to 7.5 G to reflect current conventions.

4.2 Stopping and Continuation

As seen in Section 3.1, based on our interim observation of the data, the proportion of waiverable members of the Study Group has a lower 95% confidence limit of about 72%. Thus, the overall waiver rate of lisinopril evaluees appears to be much greater than 50%.

As discussed in Sections 3.2 and 3.3, the only test cluster which could, in principle, be examined for a statistical trend was the Medical Evaluation Profile for the G tolerance test cluster. Unfortunately, this is the data which was somewhat compromised by poor compliance with the protocol. Only two of the four variables measured by this profile was deemed suitable for analysis. Even with the limited number of G tolerance evaluations performed thus far in the study, the test results indicated that, at this first interim observation, the mean value of GOR 1 for the Study Group is at least as good as that of the Control Group (in the sense that we were able to reject the hypothesis that it was not with a probability of Type I error of less than 5%). Now that the protocol compliance problems have been addressed, there is reason to hope that a more complete picture of Medical Evaluation Profile results can be achieved at future observations.

The favorable overall waiver rate, the favorable outcome thus far for GOR 1, and the absence of any observed aeromedically significant side effects of lisinopril in the Study Group are all indications in favor of the Research Hypotheses; however, the sample size limitations and protocol compliance problems found at this interim analysis preclude the feasibility of stopping for any element of the *Research Protocol* at this time.

4.3 Recruitment and Projected Completion

The projected yearly recruitment for the Lisinopril Study Group as a whole, as well as for the G Tolerance Subgroup, are shown in Figure 1. These projections are based on the rate of entry of aviators into the Study Group from November, 1992, through March, 1995.

Recruitment Statistics

Start of Study	11-Feb-94
1st Evaluation	17-Nov-92
Last Look	6-Mar-95
Yrs. of Evaluation	2.30
Yrs. of Study	1.06
No. of Subjects at Last Look	40
(No. of Subjects)/(Yrs. of Evaluation)	17.40
Projected No. of Study Group Subjects	
2nd Yr. of Study	56
3rd Yr. of Study	74
4th Yr. of Study	91
5th Yr. of Study (projected end of study)	109
6th Yr. of Study	126

No. of G-Tolerance Subjects, Last Look	9
(No. of G-Tol. Subj.)/(Yrs of Eval.)	3.92
Projected No. of G-Tolerance Subjects	
2nd Yr. of Study	13
3rd Yr. of Study	17
4th Yr. of Study	20
5th Yr. of Study (projected end of study)	24
6th Yr. of Study	28

Frequency of Recruitment

Month Ending	Number
11-Dec-92	2
11-Jan-93	0
11-Feb-93	0
11-Mar-93	0
11-Apr-93	1
11-May-93	0
11-Jun-93	1
11-Jul-93	0
11-Aug-93	0
11-Sep-93	3
11-Oct-93	2
11-Nov-93	3
11-Dec-93	5
11-Jan-94	2
11-Feb-94	0
11-Mar-94	0
11-Apr-94	2
11-May-94	1
11-Jun-94	1
11-Jul-94	0
11-Aug-94	4
11-Sep-94	2
11-Oct-94	2
11-Nov-94	3
11-Dec-94	2
11-Jan-95	1
11-Feb-95	1
11-Mar-95	2

Total	40

Figure 1. Study Group Recruitment Projections Based on Rates at the First Interim Analysis

In the following table we have, for each yearly projected Study Group Size, the number of disqualifications (due to aeromedical side effects of lisinopril) which correspond to rejection of statistical null hypotheses relevant to our research questions.

Year of Study	Number of Subjects	Maximum No. of Disqualifications for Rejecting the Hypothesis H_0: $p_{lisinopril} < p_0$ (= 0.95)	Minimum No. of Disqualifications for Rejecting the Hypothesis H_0: $p_{lisinopril} \geq p_0$ (= 0.95)
2	56	0	7
3	74	0	8
4	91	0	9
5	109	1	10
6	126	2	12

The analogous table for the G Tolerance Subgroup is as follows.

Year of Study	Number of Subjects	Maximum No. of Disqualifications for Rejecting the Hypothesis H_0: $p_{lisinopril} < p_0$ (= 0.95)	Minimum No. of Disqualifications for Rejecting the Hypothesis H_0: $p_{lisinopril} \geq p_0$ (= 0.95)
2	9	N/A	3
3	13	N/A	3
4	17	N/A	4
5	20	N/A	4
6	24	N/A	4

If a reversed trend were to develop, these last two tables indicate the minimum number of disqualifications, for each projected interim sample size, which would be required to definitively reject our research hypothesis for a given test cluster.

4.4 Summary

In this report we have described the first annual interim observation of the study group recruited under the *Research Protocol for the Use of Lisinopril in USAF Aircrew*. Our objective was to measure progress toward the goals of determining the degree to which aviators on lisinopril require individual centralized evaluation and the degree to which clinical criteria can be identified for the establishment of medical waiver evaluations by local Flight Surgeons. Our approach has been twofold: (1) we have monitored the data collection process as implemented through the *Research Protocol*, and (2) we have statistically examined the data collected to date in terms of the statistical hypotheses set forth in the protocol.

We found that the Protocol has generally been well implemented. One area in which there were some deviations from the Protocol was in G tolerance testing, where there were apparent misunderstandings about the stringency of requirements from the research perspective. Statistical analysis of the interim data revealed that the overall aeromedical waiver rate for aviators on lisinopril was well above 50%, at a 95% confidence level ($p << 0.001$), supporting continuation of the study. We also compared the G tolerance Medical Evaluation Profile data from the Lisinopril Study Group against the findings in the Control Group. Our analysis showed that, at a 95% confidence level, the performance of the Study Group was at least as good as that of the Control Group for GOR 1 ($p < 0.05$). The data for ROR-Pass, GOR 2, and GORS was too incomplete for an analysis. Likewise, the sample sizes were too small for statistical

comparisons of the proportions of normal test cluster outcomes against 95%. On the other hand, as of this interim observation of the Study Group, there were no reported cases of aeromedically significant side effects of lisinopril as outcomes in any of the test clusters.

Finally, as a result of this interim analysis, the *Research Protocol* has been changed to reflect the change in the USAF Aircrew G tolerance Training Standard from 8 G for 15 sec. to 7.5 G for 15 sec. in an upright seat. Also, a special form was developed for recording all G tolerance data required under the *Research Protocol*. This form will accompany evaluees to centrifuge testing and will be completed by the medical monitor supervising the testing. In addition, we conclude that current trends in the waiver rate and the clinical and G tolerance data indicate that continuation of the study is justified and likely to result in definitive conclusions regarding the Research Hypotheses. The study is on schedule and is yielding useful information. No other changes are suggested.

References

[1] *Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew*, USAF Armstrong Laboratory, Clinical Sciences Division, 1994.

[2] Gillingham, Kent K., Cristy M. Schade, William G. Jackson, and Larry Gilstrap. Women's G Tolerance. Aviation, Space, and Environmental Medicine, 1986; 57:745-53.

[3] Whinnery, James E. Acceleration Tolerance of Asymptomatic Aircrew with Mitral Valve Prolapse. Aviation, Space, and Environmental Medicine, 1986; 57:986-92.

[4] Woolson, Robert F. *Statistical Methods for the Analysis of Biomedical Data.* John Wiley & Sons, New York, 1987.

Appendix A: G Tolerance Evaluations

As of March 6, 1995, there were 9 members of the lisinopril study group enrolled in the G tolerance subgroup. In order to elucidate deviations from the G Tolerance Protocol, we present the data for each of these cases individually.

Case 1 (Exam Date: **19 Nov 1992).**

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	4.0	-	Relaxed	Light Loss
ROR 1	6 G/sec	2.8	15	Relaxed	Completion
ROR 2	6 G/sec	3.1	9	Relaxed	Light Loss
ROR - pass	-	2.8	-	-	-
GOR 2	0.1 G/sec	3.9	-	Relaxed	Light Loss
GORS	0.1 G/sec	6.7	-	L-1	Light Loss
Training	6 G/sec	3.0	15	GMT	Completion
Training	6 G/sec	5.0	15	L-1	Completion
Training	6 G/sec	8.0	4	L-1	LOC
Standard	6 G/sec	8.0	15	L-1	Completion
Qualified	-	YES	-	-	-

Notes: GMT = "Generalized Muscular Tensing"
Light Loss = "Reached Light Loss Criterion"

Analysis: The Lisinopril Protocol was followed. The evaluee did not achieve the Mean G Tolerance for medical evaluees given in the Protocol, and was in fact at the 1 s.d. below mean level given in the Protocol as indicative of low G tolerance. The evaluee also failed to complete the 3.1 G ROR which the Protocol presents as indicative of low G tolerance. The evaluee did attain the training standard and was rated as qualified to fly high-performance aircraft.

Case 2 (Exam Date: **23 Aug 1993**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	6.3	-	Relaxed	Light Loss
ROR 1	1 G/sec	2.8	15	Relaxed	Completion
ROR 2	1 G/sec	3.1	15	Relaxed	Completion
ROR 3	1 G/sec	3.4	15	Relaxed	Completion
ROR 4	1 G/sec	3.7	15	Relaxed	Completion
ROR 5	1 G/sec	4.0	15	Relaxed	Completion
ROR 6	1 G/sec	4.3	15	Relaxed	Completion
ROR 7	1 G/sec	4.6	15	Relaxed	Completion
ROR 8	1 G/sec	4.9	7	Relaxed	Light Loss
ROR 9	1 G/sec	4.9	7	Relaxed	Light Loss
ROR-pass	-	4.6	-	-	-
GOR 2	0.1 G/sec	5.7	-	Relaxed	Light Loss
GORS	0.1 G/sec	7.1	-	L-1	Light Loss
Training	1 G/sec	3.0	15	Relaxed	Completion
Training	1 G/sec	5.0	15	MTLE	Completion
Training	1 G/sec	7.0	15	Inadequate	Completion
Standard	1 G/sec	8.0	15	L-1	Completion
Qualified	-	YES	-	-	-

Notes: MTLE = "Muscle Tensing Lower Extremities"
Inadequate = "Attempted Maneuver but Inadequate"
Light Loss = "Reached Light Loss Criterion"

Analysis: It appears that the Lisinopril Protocol was not followed for this evaluee. While the general sequence of GORs and RORs was followed, a run type of 02 (ROR 1 G/sec), instead of 08 (6 G/sec), was listed for all RORs, including the Training Profile. This may explain the accomplishment of an extended sequence of Medical Evaluation RORs compared to the other evaluees. This given, all criteria for good G tolerance were met and the subject was rated as qualified to fly high-performance aircraft. However, a lack of adherence to the Protocol leaves in question whether the GOR levels for this evaluee can rightfully be included in comparing the Lisinopril Study Group to a Control Group.

Case 3 (Exam Date: **27 Aug 1993**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	3.6	-	Relaxed	Light Loss
ROR 1	6 G/sec	2.8	15	Relaxed	Completion
ROR 2	6 G/sec	3.1	15	Relaxed	Completion
ROR 3	6 G/sec	3.4	12	Relaxed	Subject
ROR 4	6 G/sec	3.7	10	Relaxed	Observer
ROR 5	6 G/sec	3.7	8	Relaxed	Subject
ROR 6	6 G/sec	4.0	6	Relaxed	Light Loss
ROR - pass	-	3.1	-	-	-
GOR 2	0.1 G/sec	3.6	-	Relaxed	Light Loss
GORS	0.1 G/sec	5.4	-	Inadequate	Light Loss
Training	6 G/sec	3.0	15	GMT	Completion
Training	6 G/sec	5.0	30	L-1	Completion
Training	6 G/sec	7.0	15	L-1	Completion
Standard	6 G/sec	9.0	15	L-1	Completion
Qualified	-	YES	-	-	-

Notes: Inadequate = "Attempted Maneuver but Inadequate"
GMT = "Generalized Muscular Tensing"
Light Loss = "Reached Light Loss Criterion"
Subject = "Subject Terminated Run"
Observer = "Central Observer Terminated"

Analysis: The Lisinopril Protocol was followed for this evaluee. The GOR 1 and GOR 2 levels were lower than the Low G Tolerance level given in the Protocol, but all ROR standards were achieved and the subject was rated as qualified to fly high-performance aircraft.

Case 4 (Exam Date: **8 Oct 1993**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	8.4	-	Relaxed	Light Loss
ROR 1	6 G/sec	3.0	15	Relaxed	Completion
ROR 2	6 G/sec	4.0	15	Relaxed	Completion
ROR 3	6 G/sec	5.0	12	Relaxed	Completion
ROR 4	6 G/sec	6.0	10	Relaxed	Light Loss
ROR - pass	-	4.0	-	-	-
GOR 2	-	-	-	-	-
GORS	0.1 G/sec	7.8	-	L-1	Subject
Training	6 G/sec	3.0	15	Relaxed	Completion
Training	6 G/sec	5.0	15	L-1	Completion
Training	6 G/sec	7.0	15	L-1	Completion
Standard	6 G/sec	8.0	15	L-1	Completion
Qualified	-	YES	-	-	-

Notes: Light Loss = "Reached Light Loss Criterion"
Subject = "Subject Terminated Run"

Analysis: The Lisinopril Protocol was not followed in two ways: (1) the Medical Evaluation Profile ROR step increases were not properly structured and (2) the GOR 2 run was not performed. Otherwise, all G tolerance standards were exceeded and the subject was rated as qualified to fly high-performance aircraft. Comparison of the GORS level to the GOR 2 level is not possible since GOR 2 was not performed.

Case 5 (Exam Date: **10 Dec 1993).**

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	4.5	-	Relaxed	Light Loss
ROR 1	6 G/sec	2.8	15	Relaxed	Completion
ROR 2	6 G/sec	3.1	15	Relaxed	Completion
ROR 3	6 G/sec	3.4	8	Relaxed	Light Loss
ROR - pass	-	3.1	-	-	-
GOR 2	0.1 G/sec	4.8	-	Relaxed	Completion
GORS	0.1 G/sec	7.2	-	L-1	LOC
Training	6 G/sec	3.0	15	Relaxed	Completion
Training	6 G/sec	5.0	30	L-1	Completion
Training	6 G/sec	7.0	15	L-1	Completion
Standard	-	-	-	-	-
Qualified	-	YES	-	-	-

Notes: Light Loss = "Reached Light Loss Criterion"

Analysis: The Lisinopril Protocol was followed, except that there is no record that the Training Standard was reached. GOR 1 does not attain the Protocol Mean G Tolerance for medical evaluees, but is above the 1 s.d. below the mean level for Low G Tolerance. GOR 2 is above the Mean G Tolerance. The Medical Evaluation Profile standard of 3.1 G for the ROR runs was met. As previously mentioned, attainment of the Training Standard is not recorded on the Centrifuge Evaluation Report, but the subject retained his qualification to fly high-performance aircraft.

Case 6 (Exam Date: **13 Dec 1993).**

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	6.4	-	Relaxed	Light Loss
ROR 1	6 G/sec	3.0	15	Relaxed	Completion
ROR 2	6 G/sec	3.5	15	Relaxed	Completion
ROR 3	6 G/sec	4.0	15	Relaxed	Completion
ROR 4	6 G/sec	4.5	6	Relaxed	Light Loss
ROR - pass	-	4.0	-	-	-
GOR 2	0.1 G/sec	5.5	-	Relaxed	Light Loss
GORS	0.1 G/sec	6.2	-	L-1	Light Loss
Training	6 G/sec	3.0	15	Relaxed	Completion
Training	6 G/sec	6.0	15	L-1	Completion
Training	6 G/sec	7.0	15	L-1	Completion
Standard	6 G/sec	8.0	15	L-1	Completion
Qualified	-	YES	-	-	-

Notes: Light Loss = "Reached Light Loss Criterion"

Analysis: The Lisinopril Protocol was not followed in the sense that the Medical Evaluation Profile ROR step increases were not properly structured. Aside from this, all standards for G tolerance were met by the evaluee and the subject was rated as qualified to fly high-performance aircraft.

Case 7 (Exam Date: **23 Jan 1995**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	6.06	-	Relaxed	Light Loss
ROR - pass	-	-	-	-	-
GOR 2	-	-	-	-	-
GORS	0.1 G/sec	7.5	-	Inadequate	Completion
Training	6 G/sec	3.0	15	GMT	Completion
Training	6 G/sec	5.0	30	L-1	Completion
Training	6 G/sec	7.0	15	L-1	Completion
Standard	-	-	-	-	-
Qualified	-	YES	-	-	-

Notes: Inadequate = " Attempted Maneuver but Inadequate"
GMT = "Generalized Muscular Tensing"
Light Loss = "Reached Light Loss Criterion"

Analysis: The Lisinopril Protocol was not followed for this evaluee. The Medical Evaluation Profile RORs and GOR 2 were not performed. There is also no record of attainment of the Training Standard of 8 G. GOR 1 was, however, well above the Mean G Tolerance for medical evaluees given in the Protocol, and performance was good on all other runs performed. The subject was judged by the evaluator to be qualified to fly high-performance aircraft.

Case 8 (Exam Date: **16 Feb 1995**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	6.0	-	MTLE	Completion
ROR - pass	-	-	-	-	-
GOR 2	-	-	-	-	-
GORS	-	-	-	-	-
Training	6 G/sec	5.0	15	L-1	Completion
Training	6 G/sec	6.0	15	L-1	Completion
Standard	-	-	-	-	-
Qualified	-	YES	-	-	-

Notes: MTLE = "Muscle Tensing Lower Extremities"

Analysis: The Lisinopril Protocol was not followed for this evaluee. The Medical Evaluation Profile RORs , GOR 2, and GORS were not performed. There is also no record of attainment of the Training Standard of 8 G. GOR 1 was, however, well above the Mean G Tolerance for medical evaluees given in the Protocol. The subject was judged by the evaluator to be qualified to fly high-performance aircraft.

Case 9 (Exam Date: **10 Mar 1995**).

Protocol Run	Onset Rate	Max. Level (G)	Duration (sec)	Strain	Termination
GOR 1	0.1 G/sec	5.6	-	MTLE	Completion
ROR - pass	-	-	-	-	-
GOR 2	-	-	-	-	-
GORS	0.1 G/sec	7.4	-	GMT	Completion
Training	6 G/sec	5.3	3	L-1	Observer
Training	6 G/sec	6.6	15	L-1	Completion
Standard	-	-	-	-	-
Qualified	-	YES	-	-	-

Notes: MTLE = "Muscle Tensing Lower Extremities"
GMT = Generalized Muscular Tensing"
Observer = "Central Observer Terminated"

Analysis: The Lisinopril Protocol was not followed for this evaluee. The Medical Evaluation Profile RORs and GOR 2 were not performed. There is also no record of attainment of the Training Standard of 8 G. GOR 1 and GORS were, however, well above the Mean G Tolerances for medical evaluees given in the Protocol. The subject was judged by the evaluator to be qualified to fly high-performance aircraft.

Appendix B: G Tolerance Data Form

Lisinopril Study Group
G Tolerance Testing Protocols

NAME		SSAN	CASE NUMBER
DATE OF BIRTH	GRADE	AIRCRAFT	DATE

Fitted G-suit will be worn for all runs, G-suit will be connected to regulator for only the Standard Training Profiles.

GOR2 and GORS may be accomplished during the same run.

Standard Medical Evaluation Profiles						
Protocol Run	**Run Type (Onset Rate)**	**Max. Level (G)**	**Duration Goal (sec)**	**Duration (sec)**	**Strain Goal**	**Termination (& Strain)**
* GOR 1	01 (0.1 G/sec)		-	-	Relaxed	
** ROR 1	08 (6 G/sec)		15		Relaxed	
ROR X	08 (6 G/sec)		15		Relaxed	
ROR X	08 (6 G/sec)		15		Relaxed	
ROR X	08 (6 G/sec)		15		Relaxed	
* ROR X	08 (6 G/sec)		15		Relaxed	
ROR - Pass	-		-	-	-	-
* GOR 2	01 (0.1 G/sec)		-	-	Relaxed	
* GORS	01 (0.1 G/sec)		-	-	L-1	

Standard Training Profiles						
Protocol Run	**Run Type (Onset Rate)**	**Max. Level (G)**	**Duration Goal (sec)**	**Duration (sec)**	**Strain Goal**	**Termination (& Strain)**
Training (warm-up)	08 (6 G/sec)	3.0	15		L-1	
Training (warm-up)	08 (6 G/sec)	5.0	30		L-1	
Training (optional)	08 (6 G/sec)	7.0	15		L-1	
* Standard	08 (6 G/sec)	7.5	15	PASS / FAIL	L-1	

* Represents value required for evaluation under the lisinopril research protocol.

** Suggest beginning at 2.8 G. The ROR Max. Level increment will be determined by the medical monitor. The 0.3 G increment should be used when evaluating near the expected endpoint. Larger increments, i.e. 1.0 or 0.5, may be considered for the lower level runs.

MEDICAL MONITOR'S SIGNATURE	PRINTED NAME OR STAMP

Appendix C: *Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew*

Armstrong Laboratory
Clinical Sciences Division

Research Protocol for the Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew

1. **Project-Task-Work Unit**: 7755-27-23

2. **Principal Investigator**:

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5. **Contractor**: Not applicable

6. **Project Objectives**: To determine if aviators on lisinopril for the treatment of primary hypertension require individual centralized evaluation at the Aeromedical Consultation Service or can clinical criteria be identified to establish Local Flight Surgeon's Office medical waiver evaluations.

Related questions are:

a. How long after beginning lisinopril therapy should aviators be monitored to detect 95% of the aeromedically significant side effects?

b. Can aviators on lisinopril for the treatment of hypertension be medically evaluated locally and aeromedically waived for flight duties or does detection of some medication

effects (including performance such as acceleration tolerance for high-performance aviators) require pre-waiver evaluation which are best evaluated at the Clinical Sciences Division or otherwise not locally available to the referring base.

7. **Background**: Lisinopril is a long-acting oral preparation angiotensin-converting enzyme (ACE) inhibitor. Lisinopril received Food and Drug Administration approval for the treatment of hypertension in 1987 and has been widely and safely used for that indication since that time. The beneficial effects of lisinopril in hypertensives result primarily from suppression of the renin-angiotension-aldosterone system. Inhibition of ACE results in decreased plasma angiotensin II which leads to decreased vasopressure activity and to decreased aldosterone secretion. Lisinopril is absorbed in the gastrointestinal tract and is metabolically active. It is excreted unchanged by the kidney. Studies in rats indicate that lisinopril crosses the blood-brain barrier poorly. Radioactively tagged lisinopril in pregnant rats was found in the placenta but not in the fetuses.

Large clinical trials of lisinopril established its effectiveness for the treatment of hypertension (n = 3,270).[5,15] Metabolic effects appear to be minimal and no renal failure has been noted with prolonged therapy (n = 1,104). [20,26] ACE inhibitors as a class of drugs decrease systemic vascular resistance, blood pressure and improve cardiac functioning while maintaining or enhancing perfusion of the kidneys, brain and heart.[30] ACE inhibitor therapy decreases left ventricular hypertrophy.[11] Cinotti, et al, reported that the incidence of side effects were limited in a clinical trial of 100 subjects and that no case required withdrawal of lisinopril.[6]

In comparison clinical trials for the treatment of hypertension, lisinopril proved more effective than hydrochlorothiazide in a 52-week study[21] and demonstrated effectiveness in another study without major side effects reported.[22,24] In a double-blinded, randomized, parallel-group multicenter trial of 340 patients with hypertension, the side effect profile of lisinopril was not different from that of the placebo group and adverse effects were few and mild.[29]

Some laboratory abnormalities have been reported. One study reports the rare occurrence of glycosuria;[23] another study reports an increased blood urea nitrogen, serum creatinine and plasma potassium (n > 1,000) but notes that these effects were fewer than other antihypertensive medication.[25] In another study, Espinel, et al, studied 97 subjects, 47 on lisinopril, and reported no laboratory abnormalities.[7]

Systemic effects of lisinopril have been evaluated clinically. Angioedema of the face and neck is the most severe reported clinical complication. Jain reports on five cases of this untoward side effect, four in patients treated with enalapril, an ACE inhibitor, and one in a patient treated with lisinopril. Obesity, previous head and neck surgery or a history of intubation appears to be a significant cofactor in these patients.[19] Cough has been described as an annoying side effect of all ACE inhibitors and usually appears within one hour to one week after beginning therapy. Incidences of this side effect are similar to all the drugs in the class of ACE inhibitors.[2,17,34] Overall quality of life was studied by Frimodt-Moeller, et al, using the General Health Questionnaire. They noted the quality of life was significantly improved two months after discontinuing thiazide therapy and beginning lisinopril therapy and there were fewer withdrawals on lisinopril as compared to metoprolol (a beta-blocker) (n = 360).[9,24]

The effects of antihypertensive treatment on G tolerance is of significant aeromedical concern.[3,12] This has not been well elucidated in the literature. Paul and Gray studied seven normotensive and randomized them to placebo or captopril, an ACE inhibitor, and evaluated their +Gz tolerance.

They found decreased tolerance in the treated subjects.[27] This is the expected result in normotensives with a drug-induced decreased systemic vascular resistance.[14,16,35] This will be the first study of adequately treated hypertensives with +Gz tolerance testing. Webb, et al, described the unpredictability of fighter pilot's G tolerance using anthropometric and physiologic variables. They studied 1,343 high-performance pilots and found that relaxed G tolerance was inversely correlated with age, weight and diastolic blood pressure. Correlation coefficents either as single variables or in a multivariable model failed to demonstrated a value of greater than 0.35. The only consistent prediction of G tolerance was the anti-G straining maneuver.[32] Whinnery looked at the medical consideration of G-LOC. He concluded that there is no indication that G-LOC episodes have any associated long-term or persistent psychophysiological sequelae.[34] The potential exists that lisinopril therapy affects +Gz tolerance.

8. **Relevance to the Air Force**: Air Combat Command and Air Force Materiel Command have requested Armstrong Laboratory to study an ACE inhibitor for the treatment of hypertension in aviators. ACC noted that in 1990 they had 55 aviators with hypertension who were not controlled or poorly controlled with the Hydrochlorothiazide (HCTZ) diuretic. Air Force wide it is expected that there are greater than 200 hypertensive aviators who could benefit from lisinopril therapy. USAF/SGPA requested that a plan be developed to evaluate aviators on a medication other than HCTZ for waiver. A plan to evaluate those aviators was developed by the Clinical Sciences Division (attachment 2). This protocol will delineate an organized scientific plan to obtain, organize, analyze and then report the information gathered during the course of aeromedical occupational examination at the Clinical Sciences Division of Armstrong Laboratory to the USAF Surgeon General for a refinement of regulatory directives.

Currently, there are only two medications available to local flight surgeons for the treatment of hypertension. Aviators controlled with HCTZ may obtain a waiver after a short period of grounding and a local evaluation. If local flight surgeons desire a different medication, a centralized evaluation at the Clinical Sciences Division is required. Lisinopril is the only other antihypertensive medication currently considered for waiver.

Thiazide diuretics are the only anti-hypertensives avilable locally for the treatment of primary hypertension in USAF aircrew. Diuretic therapy was the medical standard of care for the treatment of hypertension when that policy was instituted. Currently, there are many new classes of medication to treat this condition. Thiazide diuretics' main effect is decreasing intra-vascular volume, and often have untoward side effects of increasing cholesterol and producing electrolyte imbalances.

9. **Impact Statement**:

If this study is not done :

a. Hypertensive aviators will continue to be placed on HCTZ or they will need to recieve an evaluation at the Clinical Sciences Division.

b. Alternative therapy to thiazide or thiazide combinations will not be locally available. The untoward side effects of thiazide will be present in some aviators on thiazides.[36] Medical choices to treat aviators for hypertension will be limited to diuretic therapy alone, this will result in fewer aviators flying on waiver and the loss of trained and experienced aviators for the Air Force.

10. **Experimental Plan**:

a. Study Design: This research is a prospective cohort study using established controls. This is an observational study. This study does not evaluate the efficacy or the effectiveness of the treatment of hypertension with lisinopril. The six hypotheses listed below result from aeromedical clinical concerns and literature review. All of the study subjects will be entered after their hypertension is therapeutically controlled. Data collected from participants during aeromedical occupational evaluation of aviators on lisinopril will be collected, organized, analyzed and reported. Systematic analyses of the data provided by aeromedical evaluations will provide a basis for quantativlely driven aeromedical recommendations regarding future regulatory guidance concerning USAF aviators on lisinopril.

Control data used in the analysis of this study could be considered external, since the control data were not collected under the supervision of the investigator. External control data, if taken from other institutions, often adds to the potential of, difficult to account for, bias adding to the study. Comparing different populations on a single or multiple variables may result in systematic error (bias) which cannot be well controlled for in even the most rigorous statistical analyses. The control data utilized in this study is retrospective data from our organization.

Control data used in our analysis is robust and from similar populations; USAF aviators evaluated at the Clinical Sciences Division and recommended to return to fly. Acceleration data are from published acceleration tests derived from normotensive aviators evaluated on the Brooks AFB centrifuge. This control group is arguably the best control group since it is a random subset of healthy USAF aviators, the information was gathered at this institution, and there is limited potential for confounding due to medication or other potentially biasing effects. The acceleration performance question is not the effect or performance of the medication but rather the individual performance of the therapeutically controlled aviator compared to a normotensive qualified aviator.

The validity of our control data is strengthened since the information was collected at this institution in recent years. It is weakened somewhat due to the lack of randomization. Bailar writes in Medical uses of Statistics of the use of external control and states that five interrelated features can add to the strength of studies using external controls.[1]

"... (1) an intent by the investigator, expressed before the study, that the treatment will affect the outcomes reported; (2) planning of the analysis before the data are generated; (3) articulation of a plausible hypothesis before the results are observed; (4) a likelihood that the results would still have been of interest if they had been "opposite" in some sense; and (5) reasonable grounds for generalizing the results from the study subjects to a substantially broader group of patients."

This primarily deals with clinical trials but the cautionary role is useful in determination of validity issues in this study. The strength of this study is derived from the prospectively planned methodology and the appropriateness of the control group.

b. Limitations of this study: This study is designed to test the six hypotheses listed below. The possibility exists that there may be other parameters or clinical features missed by the focused examination. This study is designed to analyze the clinical data gathered during the Clinical Sciences Division occupational evaluation. Due to the relative smallness of the expected sample size, rare events will not be quantifiable.

c. Research questions to be investigated:

1) Are there detectable aeromedically significant vestibular abnormalities present in aviators with hypertension therapeutically controlled with lisinopril?

2) Are there detectable aeromedically significant audiometric abnormalities present in aviators with hypertension therapeutically controlled with lisinopril?

3) Do aviators with hypertension therapeutically controlled with lisinopril have an increased risk of aeromedically significant coronary artery disease?

4) Do aviators with hypertension therapeutically controlled with lisinopril have an increased risk of aeromedically significant ophthalmologic disorder?

5) Do aviators with hypertension therapeutically controlled with lisinopril who fly high-performance aircraft have a decreased G tolerance compared to normotensive aviators on no medication who fly high performance aircraft?

6) Do aviators with hypertension therapeutically controlled with lisinopril demonstrate laboratory abnormalities in blood and/or urine samples?

d. Testing: Evaluations at the Clinical Sciences Division: Aeromedical evaluations shall include an examination to identify medication side effects and to delineate and quantify selected performance testing: The clinical evaluation listed represents the battery of tests and observations currently required by USAF/AFMOA for the consideration of waiver for aviators on lisinopril for hypertension. This evaluation has been reviewed and was determined to be the aeromedical standard of care for hypertensive aviators on lisinopril evaluated at the Clinical Sciences Division by the Clinical Sciences Division Quality Assurance Committee.(attachment 2)

e. Subject pool: Potential Subjects: Lisinopril protocol subjects will be drawn from all consenting aviators who are evaluated at the Clinical Sciences Division for the treatment of hypertension with lisinopril. This study is open to all aviators evaluated, female and male.

All Clinical Sciences Division Evaluees on lisinopril will be offered inclusion in this study. The goals, purpose and expected duration will be discussed with them, their questions will be answered and if they agree to participate, the attached study consent form will be completed and signed (attachment 1).

f. Duration of the Study: The study is intended to be carried out over five years. Since the study is designed to test the study questions stated in Section 10.c of this protocol, the data will be analyzed semi-annually the first year and annually thereafter to determine

approximately how many subjects will be required to adequately test each hypothesis and, if given the current rate of subject recruitment and follow-up, that number will be reached within the planned five-year duration of the study. The study will be terminated when this number is reached or, if data analysis by the investigators, it is statistically determined that the stated research question cannot be supported by the data. The study will be stopped if greater than 50% of aviators are denied waiver post ACS evaluation with an alpha error set at 0.05 and beta error of 0.20 (power = 0.80).

g. Statistical Methods: Three questions to which known answers might affect the continuation of all or parts of the Lisinopril study and which will be addressed statistically in this study are:

(1) Is the overall yield of waiverable aviators among the study subjects below 50%?

(2) For any particular cluster of tests (G-tolerance, coronary artery disease, etc.), is the prevalence of a disqualifying condition greater than or less than 5%?

(3) For any test that yields a continuous response, is the mean value for Lisinopril subjects different from the mean of aeromedically "normal" subjects?

The methods described below to answer these three questions could easily be adjusted to take into account other null hypotheses if so desired (such as 60% in Question 1).

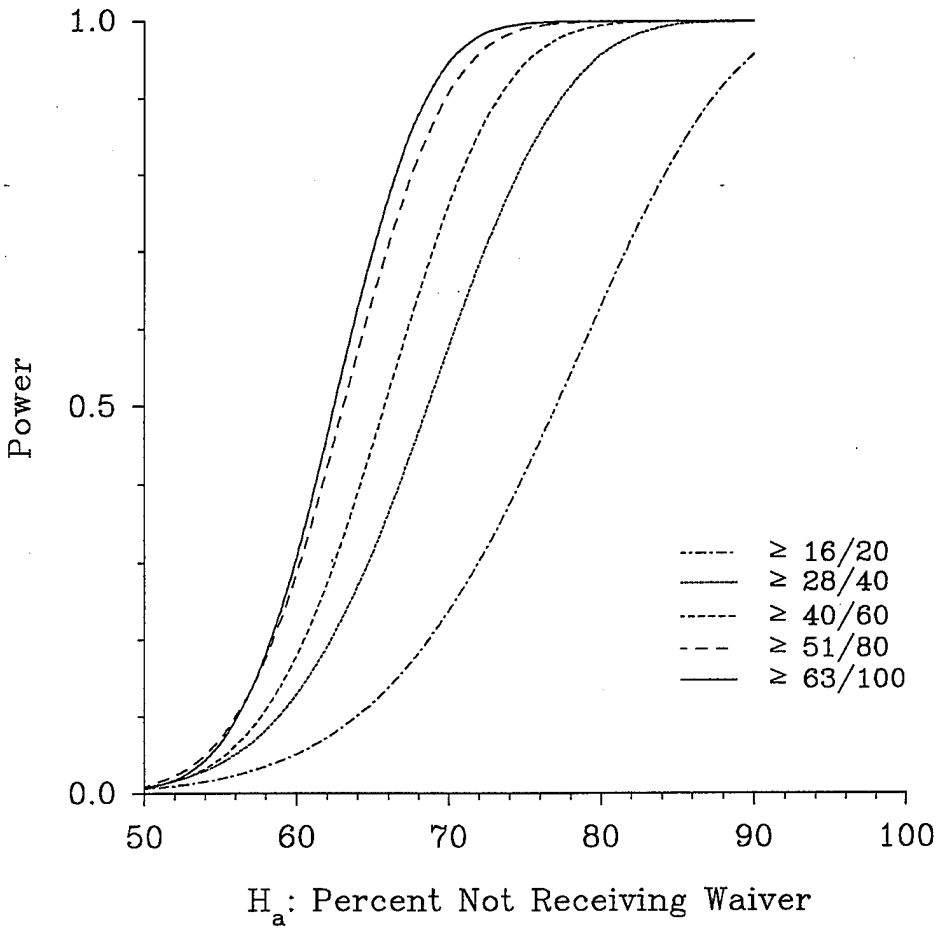

Figure 1. Power of five sequential stopping rules for accepting H_a: percent disqualified > 50%. Overall Type I error rate = 5%.

Figure 1 addresses power for a test of the null hypothesis (H_0) that the percent of subjects on Lisinopril who are found to be waiverable will be at least 50% vs. the 1-tail alternative hypothesis (H_a) that the percent not receiving waiver will exceed 50%. H_0 will be tested sequentially after 20, 40, 60, 80, and 100 subjects have completed the waiver process, and an unacceptably large number of disqualifications at any of these five steps will result in rejection of H_0. The five critical values for rejection are, respectively, 16 disqualifications out of the first 20 subjects, 28 of the first 40, 40 of the first 60, 51 of the first 80, or 63 of the first 100. The overall Type I error rate for the test does not exceed 5%. In terms of power, Figure 1 shows, for example, that if the overall disqualification rate is 70%, then the probability that H_0 will be rejected after 20 subjects is only about .23, but that probability rises to about .60 after 40 subjects and .80 after 60 subjects.

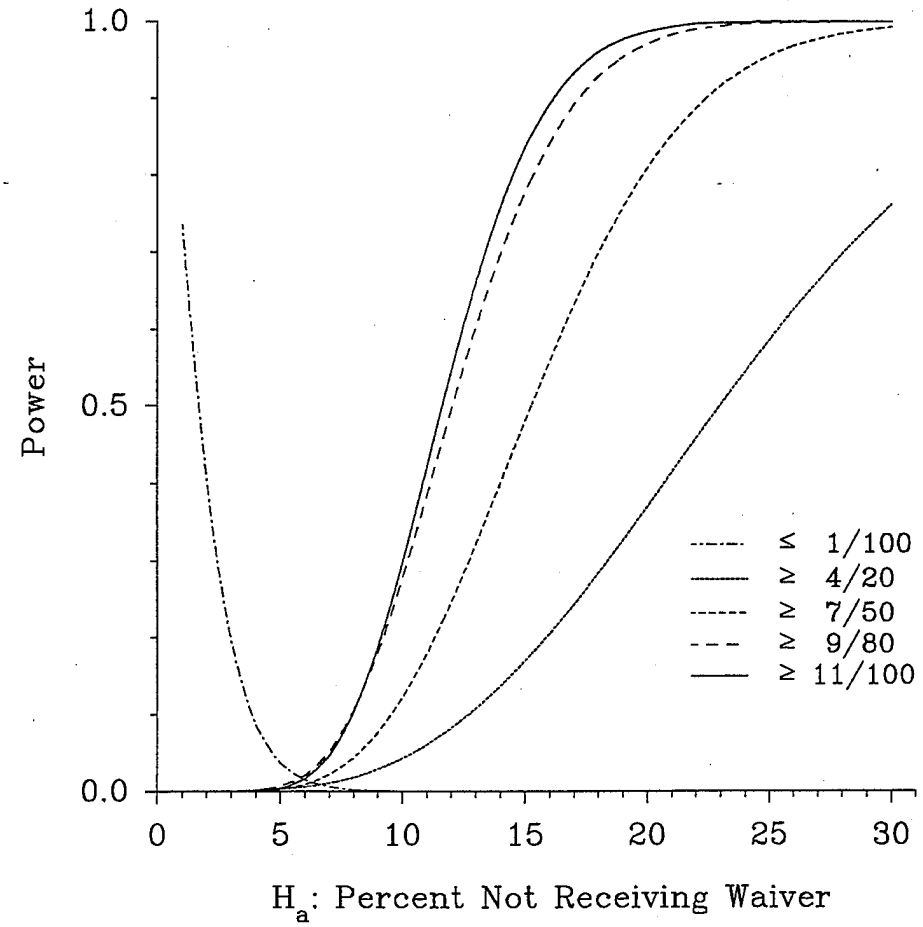

Figure 2. Power of five sequential stopping rules for accepting H_a: prevalence of disqualifying result on a particular test differs from 5%. Overall Type I error rate = 10%.

Figure 2 addresses power for a test of the null hypotheses (H_0) that the percent of subjects on Lisinopril found to be waiverable for a particular cluster of medical tests (such as the centrifuge, coronary artery disease, etc.) will equal 95% vs. the 2-tail alternative hypothesis (H_a) that the percent disqualified will differ from 5% (the assumed prevalence of abnormality among aviators not on Lisinopril). These tests will be 2-tailed so that rejection of H_0 can guide a decision to either discontinue or make permanent the particular cluster of exams on Lisinopril aviators seeking a waiver to fly. H_0 will be tested sequentially after 20, 50, 80, and 100 subjects have completed the waiver process. Too few or too many disqualifications at any of these four steps will result in rejection of H_0. The critical values that lead to a conclusion that the disqualification rate exceeds 5% are 4 (or more) disqualifications out of the first 20, 7 (or more) out of the first 50, 9 (or more) out of the first 80, and 11 or more out of the first 100. The critical value that leads to a conclusion that the disqualification rate is less than 5% is 1 disqualification of the first 100. The Type I error rate for this sequence of statistical tests for particular cluster of medical procedures is less than 10%. In terms of power, Figure 2 shows, for example, that if the disqualification rate for a related cluster of procedures is 20%, then the probability that H_0 will be rejected after 20 subjects is about .40, but the probability rises to over .80 after 50 subjects and over .95 after 80 subjects.

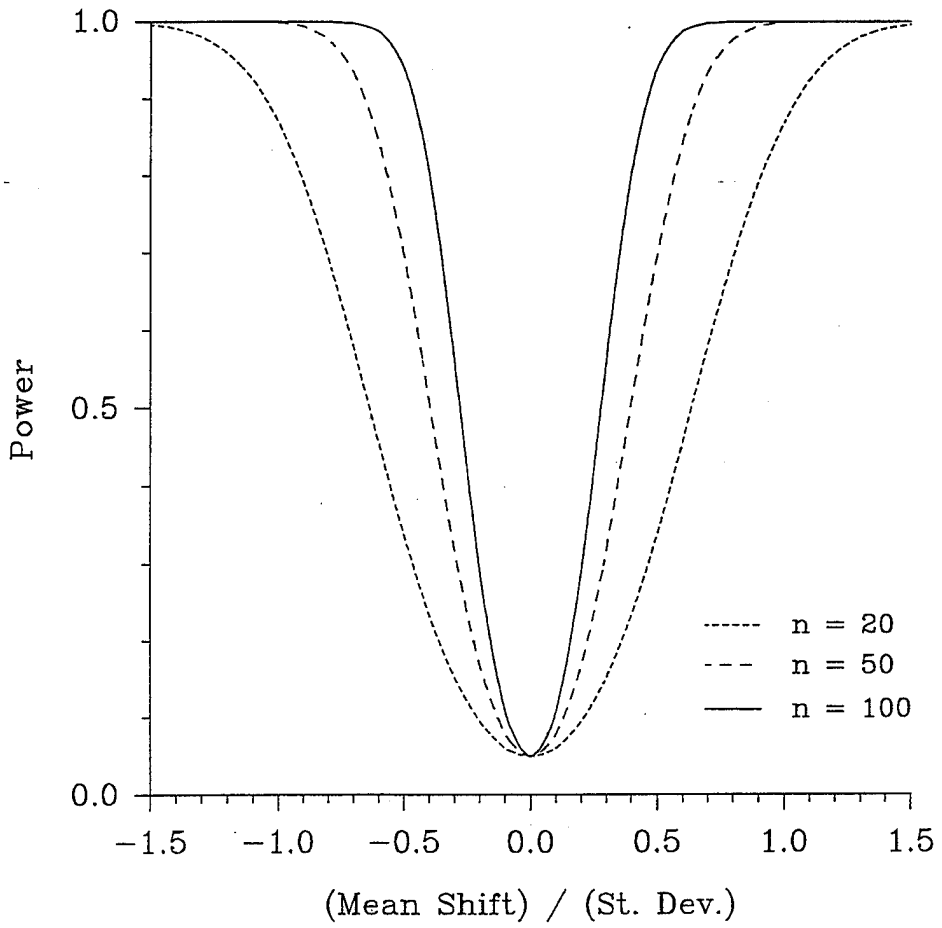

Figure 3. Power curves for 2-tail, unpaired t-tests with group sample size of 20, 50, and 100, and Type I error rate = 5%.

Figure 3 shows power curves for 2-tail unpaired t-tests with equal sample sizes of 20, 50, and 100 observations for testing a null hypothesis (H_0) that the mean response for Lisinopril subjects on a particular procedure (such as G-tolerance for the rapid-onset run) does not differ from the mean value for "normal" subjects. "Normal" here will generally mean a waiverable population of flyers seen historically at the Armstrong Laboratory. The mean difference is measured in units of standard deviations since that will change for each procedure. The range of differences is from -1.5 to +1.5 standard deviations, which represents a wide spectrum of differences. The group sample size will also be different for each procedure, depending not only on how many Lisinopril subjects are involved, but also on how many subjects were used to establish the mean for "normals". Thus, the curves represent a lower bound for power when the smaller of the two groups contains n subjects. The Type I error rate for these calculations was set at 5%. In terms of power, Figure 3 shows, for example that if the mean difference between Lisinopril subjects and "normal" subjects is one-half of a standard deviation, then the probability that the t-test will be statistically significant at the .05 level when n = 50 is about .70.

h. Data storage: Data will be recorded and maintained on the VAX6020 located within AL/AOC. This hardware hosts the Rdb™ relational database software. This software provides advanced data security as part of its design features, and hosts all of our current archived evaluee data. Record access can be restricted to particular users, so that identifiable data on any study participant cannot be obtained by unauthorized users or released without the individual's express written consent. Any data recorded using desktop, laptop, notebook or other computers will be recorded directly onto appropriate mini floppy diskettes without backup to the computer's resident hard disk. Microcomputer data files will be labeled using the first four letters of the subject's last name (or underscore to indicate blanks in the event that the last name has fewer than four letters) and the last four numbers of the subject's social security account number. The extension will indicate the test recorded in that file. The diskettes will be removed from the computer only by the examiner and placed in a locked container until they can be uploaded to Rdb™. When all the data from a given floppy have been uploaded, the floppy will be reformatted to erase all usable references to the original data.

i. Safety Precautions and Measures: All medical evaluation and procedures accomplished at the Clinical Sciences Division and the Crew Technology Directorate are accomplished by personnel assigned to their respective organizations. Both organizations have Quality Assurance committees which review professional personnel qualifications and procedural compliance to appropriate regulatory directives. The medical data that will be collected for this research will be extracted from medical records with the explicit written permission of the individuals evaluated.

11. **Medical Risk Analysis**:

a. Information briefed to subjects.

1) All subjects will be briefed on the nature, purpose and goals of this research project and will acknowledge by signing the Lisinopril Study consent form (attachment 1).

2) Medical evaluation procedures accomplished as part of the subjects' aeromedical evaluation that pose any potential medical risks will be briefed prior to the accomplishment of that procedure, and a signed consent form will be placed in the ACS medical record. These procedures include exercise treadmill on all evaluees and centrifuge testing on high performance aviators.

b. Benefit vs. risk:

1) Individual study participants accept no additional personal or medical risk by consenting to inclusion into this study. No additional testing to the existing aeromedical occupational ACS evaluation is required.

2) The benefit for the individual study participant is that the possibility exists that, after the results of the study are presented to the USAF/SG, a policy requiring less comprehensive examination for hypertension in aviators treated with lisinopril will be directed. Additionally, if any medical condition is detected during the course of their evaluation, the subjects will be informed of the

medical findings and appropriate medical care for the previously undiscovered condition will be recommended.

Attachments:
1. Voluntary Consent 'The Evaluation of Medical Waiver Requirements for the Use of Lisinopril in USAF Aircrew' **(NOT INCLUDED IN INTERIM REPORT)**
2. Armstrong Laboratory Clinical Sciences Division 'Aeromedical Evaluation for Aircrew on Lisinopril for Hypertension' with attachments

REFERENCES

1. Bailar JC, Mosteller F, eds. Medical uses of statistics, 2nd ed. Boston: NEJM, 1992.

2. Barnes JM, Barnes NM, Costall B, Coughlan J, Kelly ME, Naylor RJ, Tomkins DM, Williams TJ. Angiotensin-converting enzyme inhibition, angiotensin, and congition. J. Cardiovasc. Pharmacol. 1992;19:S63-71.

3. Barnes, JM, Barnes NM, Costall B, Horovitz ZP, Ironside JW, Naylor RJ, Williams TJ. Angiotensin II inhibits cortical cholinergic function: implications for cognition. J. Cardiovasc Pharmacol. 1990;
16(2):234-8.

4. Bulpitt CJ, Fletcher AE. Cognitive function and angiotensin-converting enzyme inhibitors in comparison with other antihypertensive drugs. J. Cardiovasc. Pharmacol. 1992;19:S100-4.

5. Cameron HA, Higgins TJ. Clinical experience with lisinopril; observations on safety and tolerability. J. Hum. Hypertens. 1989;3:177-86.

6. Cinotti GA, Bossini A, Cagli V, Corea L, DiVeroli C, Morabito S, Pierucci A, Porcellati C, Savino K, Timio M. Multicenter clinical study of the antihypertensive activity of lisinopril. Minerva Med. 1989;80(1):53-63.

7. Espinel CH, Williams JL, Coughlin SS. Enalapril and lisinorpril in the treatment of mild to moderate essential hypertension. Clin Ther. 1990;12(2):181-90.

8. Feman SS, Mericle RA, Reed GW, May JM, Workman RJ. Serum angiotensin converting enzyme in diabetic patients. Am. J. Med. Sci. 1993;305(5):280-4.

9. Frimodt-Moeller J, Poulsen DL, Kornerup HJ, Bech P. Quality of life, side effects, and efficacy of lisinopril compared with metoprolol in patients with mild to moderate essential hypertension. J. Hum. Hypertens. 1991;5(3):215-21.

10. Genest JJ, McNamara JR, Salem DN, Schaefer EJ. Prevalence of risk factors in men with premature coronary artery disease. Am. J. Cardiol. 1991;67(15):1185-9.

11. Gilbert BW. Ace inhibitors and regression of left ventricular hypertrophy. Clin. Cardiol. 1992;15(10):711-4.

12. Gillingham KK, Fosdick JP. High-G training for fighter aircrew. Aviat. Space Environ. Med. 1988;59:12-9.

13. Gillingham KK, Schade CM, Jackson WG, Gilstrap LC. Women's G tolerance. Aviat. Space Environ. Med. 1986;57:745-53.

14. Gillingham KK. G-tolerance standards for aircrew training and selection. Aviat. Space Environ. Med. 1987;58:1024-6.

15. Herpin D, Conte D. Assessment of the antihypertensive effect of lisinopril using 24-hour ambulatory monitoring. J. Hum. Hypertens. 1989;3:11-15.

16. Hull DH, Wolthuis RA, Gillingham KK, Triebwasser JH. Relaxed +Gz tolerance in healthy men: effect of age. J. Appl. Physiol.: Respirat. Environ. Exercise Physiol. 1978;45(4):626-29.

17. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin-converting enzyme inhibitor therapy: a review of the literature and pathophysiology. Ann. Intern. Med. 1992;117(3):234-42.

18. Jackson WE, Holmes DL, Garg SK, Harris S, Chase HP. Angiotensin-converting enzyme inhibitor therapy and diabetic retinopathy. Ann. Ophthalmol. 1992;24(3):99-103.

19. Jain M, Armstrong L, Hall J. Predisposition to and late onset of upper airway obstruction following angiotensin-converting enzyme inhibitor therapy. Chest. 1992;102(3):871-4.

20. Karlberg BE, Rosenqvist U. Antihypertensive and hormonal effects of lisinopril, a new angiotensin converting enzyme (ACE) inhibitor in patients with renovascular hypertension. Acta. Med. Scand. Suppl. 1986;714:33-42.

21. Kochar MS, Bolek G, Kalbfleisch JH, Olzinski P. A 52-week comparison of lisinopril, hydrochlorothiazide, and their combination in hypertension. J. Clin. Pharmacol. 1987;27(5):373-7.

22. Mehta J, Lopez LM, Thorman AD. Lisinopril versus lisinopril plus hydrochlorothiazide in essential hypertension. Am. J. Cardiol. 1988;61(10):803-6.

23. Milavetz JJ, Popovtzer MM. Angiotensin-converting enzyme inhibitors and glycosuria. Arch. Intern. Med. 1992;152(5):1081-3.

24. Morlin C, Baglivo H, Boeijinga JK, Breckenridge AM, Clement D, Johnston GD, Klein W, Kramer R, Luccioni R, Meurer KA. Comparative trial of lisinopril and nifedipine in mild to severe essential hypertension. J. Cardiovasc. Pharmacol. 1987;9:S49-52.

25. Moyses C, Higgins TJ. Safety of long-term use of lisinopril for congestive heart failure. Am. J. Cardiol. 1992;70(10):91C-97C.

26. Murray NH. Duration of angiotensin-converting enzyme inhibition: implication for tolerability. Cardiology. 1991;79:22-9.

27. Paul MA, Gray GW. The effect of captopril on +Gz tolerance of normotensives. Aviat. Space Environ. Med. 1992;63:706-8.

28. Simons LA. Triglyceride levels and the risk of coronary artery disease: a view from Australia. Am. J. Cardiol. 1992;70(19):14H-18H.

29. Swedish Lisinopril Study Group. Lisinopril combined with atenolol in the treatment of hypertension. J. Cardiovasc. Pharmacol. 1991;18(3):457-61.

30. Thind GS. Angiotensin converting enzyme inhibitors: comparative structure, pharmacokinetics, and pharmacodynamics. Cardiovasc. Drugs Ther. 1990;4(1):199-206.

31. Tuomilehto J, Wikstrand J, Warnold I, Olsson G, Elmfeldt D, Berglund G. Coronary Artery Disease can be prevented by antihypertensive therapy: experiences from the MAPHY Study. J. Cardiovasc. Pharmacol. 1990;16:S75-6.

32. Webb JT, Oakley CJ, Meeker LJ. Unpredictability of fighter pilot G tolerance using anthropometric and physiologic variables. Aviat. Space Environ. Med. 1991;62(2):128-35.

33. Whelton A. Application of ambulatory blood pressure monitoring to clinical therapeutic decisions in hypertension. J. Hypertens. Suppl. 1991;9(1):S21-5.

34. Whinnery JE. Medical considerations for human exposure to acceleration-induced loss of consciousness. Aviat. Space Environ. Med. 1991;62(7):618-23.

35. Whinnery JE. Acceleration tolerance of asymptomatic aircrew with mitral valve prolapse. Aviat. Space Environ. Med. 1986;57:986-92.

36. Zemel PC, Sowers JR. Relation between lipids and atherosclerosis: epidemiologic evidence and clinical implications. Am. J. Cardiol. 1990;66(21):71-121.

Armstrong Laboratory Clinical Sciences Division

Aeromedical Evaluation for Aircrew on Lisinopril for Hypertension

1. **Potential Evaluees:** Lisinopril evaluees should be drawn from aviators who are thiazide and thiazide combination drug treatment failures or individuals who have been placed on lisinopril prior to a thiazide trial for locally identified medical indications. In addition, evaluees referred from other services could be evaluated using this evaluation protocol. Therefore all hypertensive aircrew, rated and non rated, USAF or from other services could and should be considered for potential inclusion into this drug treatment evaluation plan.

2. **Side Effect Incidence**:

	Lisinopril (n=2003) %	Placebo[1] (n=207) %
Dizziness	6.3	1.9
Headache	5.3	1.9
Fatigue	3.3	1.0
Diarrhea	3.2	2.4
Upper respiratory symptoms	3.0	0.0
Cough	2.9	1.0
Hypotension	1.8	0.5
Rash	1.5	0.5
Orthostatic effects	1.4	1.0
Asthenia	1.3	1.0
Vomiting	1.3	0.5
Dyspepsia	1.0	0.0
Paresthesia	0.8	0.0

Other side effects include neutropenia, agranulocytosis, angioedema, hyperkalemia, and teratogenesis.

3. **Logistics:** Equipment and Facilities: Existing funds, equipment and facilities are sufficient to complete this study at a rate of not more than two evaluation per week, 48 weeks per year, including:

a. Technicians in local flight surgeon's office to accomplish 5-day BP check;

b. Local TDY funds to refer evaluees to the USAF Aeromedical Consultation Service (ACS), Brooks AFB, Texas, for initial and follow-up visits the same as any other referral;

c. Clinical laboratory at AL/AOCF to perform assays for serial comparison;

1. Physicians' Desk Reference (PDR), 46th ed, Montvale NJ, p. 1540, 1992.

d. Computer, statistical and epidemiological support at AL/AOCR/Clinical Research Coordination Center to capture, store, and report results;

e. AL/AOC flight surgeons to verify effectiveness of treatment and check clinically for possible side effects;

f. AL/AOCI staff and facilities to perform and interpret resting and symptom-limited exercise ECG, 24-hour Holter monitor, echocardiogram, and pulmonary function tests;

g. AL/AOCO staff to perform ocular examinations;

h. AL/AOCFO staff to administer and interpret rotary chair Vestibular Ocular Response (VOR), eye tracking and audiometrics;

i. AL/AOCFR staff to accomplish radiographic studies:

j. AL/CFT human centrifuge and staff to perform and interpret acceleration performance tests.

4. **Evaluee Exclusion Criteria:** The following criteria are each sufficient to **exclude** an evaluation:

a. Any non-waiverable condition other than uncontrolled hypertension;

b. Secondary hypertension;

c. Serum creatinine >1.4 mg/dl;

d. Non-aviators;

e. Established mandatory date of separation/retirement within one year;

f. Disqualified for world-wide duty because of excessive body fat;

g. Pregnant or trying to become pregnant.[2,3]

5. **Evaluee Inclusion Criteria:** Protocol evaluee must meet one of these inclusion criteria.

a. The local base flight surgeons have the primary responsibility for the medical care of the aviators. If, in their opinion, after possible consultation with local or otherwise available medical consultation,

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2. Mehta N, Modi N. ACE inhibitors in pregnancy. Lancet 2(8654):96-97, 1989.

3. Pipkin FB, Baker PN, Symonds EM. ACE Inhibitors in Pregnancy. Lancet 2(8654):96-97, 1989.

d. **Step 4**: If both the average 5-day SBP is <141 mmHg and the average 5-day DBP is <90 mmHg and there are no aeromedically significant side effects, then the evaluee is referred to the USAF Aeromedical Consultation Service. The base flight surgeon continues to evaluate the aviator weekly for side effects until the evaluee actually departs the referring base for the USAF Aeromedical Consultation Service.

e. **Step 5**: At the USAF Aeromedical Consultation Service, evaluees shall be examined and undergo performance tests. High-performance Aviators will undergo centrfuge testing. If they perform to minimum standards IAW TARF Reg 51-17 then they can be considered for an unresricted FC II waiver. To be considered for an unrestricted waiver, USAF tanker/transport/bomber aviators shall undergo acceleration tolerance testing. Aviators who fail centrifuge testing shall only be considered for categorical waivers recommendations restricted to non-high performance aircraft (FC IIC). The minimum acceleration tolerance to receive an unrestricted wavier is the TARF standard of 7.5 $+G_Z$ for 15 seconds with a G-suit and proper straining maneuver in an upright seat. Each aviator will have up to three attempts on different days to attain this performance standard. Aviators not meeting this standard will be recommended for a categorical waiver and restricted to non-high performance aircraft.

f. **Step 6**: The results of performance tests conducted by the Crew Technology Division shall be attached to the ACS aeromedical summary and forwarded to HQ AFMOA/SGPA if the evaluee is active USAF, Air Guard, or AF Reserve and to any other appropriate waiver authority if the aviator is from other than the USAF. Recommendation for medical waivers shall not be contingent upon "passing" all the tests. Rather, all data shall be considered together as in any other flyer referred to the USAF Aeromedical Consultation Service. The issue shall **not** be whether the flyer is perfect, but whether the flyer as a whole is at increased risk to flying safety or mission completion relative to a normotensive flyer taking no medication.

g. **Step 7**: Waiver authority, including waiver renewals, is retained by HQ AF/SG for all USAF active duty, Air Guard, and USAF Reserve personnel. Temporary waivers are to be be granted for one year or less. Waived evaluees will be re-evaluated by the USAF Aeromedical Consultation Service prior to expiration of the temporary waiver. Each time a waived aviator on lisinopril is medically disqualified from flying duties, the USAF Surgeon General (AFMOA/SGPA) will review all aviators currently on waivers for lisinopril, if the USAF Surgeon General continues waivers for lisinopril.

7. **Not Human Experimentation**: This protocol describes the use of an approved medication for use in an occupationally defined group of individuals. This is medical care and standard of care aeromedical evaluation of an occupationally based group, not human experimentation.

8. **Evaluations at the Clinical Sciences Division**: Aeromedical evaluations shall include both an examination to identify medication side effects and to delineate and quantify selected performance testing:

a. The Clinical Sciences Division of the Aerospace Medicine Directorate of the Armstrong Laboratory will accomplish:

1) Flight medicine evaluations, including medical history, with a review of outpatient record, a review of systems, and a physical exam;

2) Daily indirect, seated, blood pressure reading;

3) ACS clinical pathology laboratory screen to include; CBC with differential, platelet count, fasting glucose, potassium, calcium, creatinine, uric acid, total cholesterol, HDL cholesterol, triglyceride, total bilirubin, SGPT, SGOT, alkaline phosphatase, GGT, sedimentation rate, BUN and a routine urinalysis,;

4) Diagnostic radiology, including PA and lateral chest x-rays, on all evaluees and a cardiac fluoroscopy if male evaluee's age is >35 years, cardiac fluoroscopy should not be accomplished on female aviators;

5) Audiology, including pure-tone audiometry and tympanometry;

6) An oculovestibular evaluation, including harmonic oscillation, optokinetic test, smooth pursuit and saccadic tracking;

7) Ophthalmologic exam, including cycloplegic refraction, intraocular tonometry, slit lamp exam, visual fields by confrontation, stereopsis, color perception, ocular motility, and contrast sensitivity;

8) Symptom-limited treadmill exercise tolerance test, echocardiography, 24-hr ambulatory ECG monitoring, and pulmonary function tests.

b. Crew Technology Directorate, Acceleration Branch will accomplish medical evaluation centrifuge testing: evaluees will undergo G-tolerance testing on the Armstrong Laboratory human centrifuge located in Building 170, Brooks AFB, TX. This testing will be done to determine whether use of the drug being investigated has any deleterious effect on the ability of aircrew to perform in the sustained high-G environment. Evaluees will be exposed on the centrifuge to the Standard Medical Evaluation G profiles (attachment 1) which consist of the following:

1) A gradual-onset (0.1G/sec) run to the visual end-point, with evaluee relaxed (GOR 1)

2) A series of rapid-onset (6 G/sec) runs lasting 15 seconds each at predetermined G levels, terminating when the visual end-point is reached, with evaluee relaxed (RORs)

3) A second gradual-onset run, to the visual end-point, with evaluee relaxed (GOR 2)

4) A gradual-onset run to the visual end-point, with evaluee performing an L-1 anti-G straining maneuver (GORS)

In the above four Standard Medical evaluation G profiles, the evaluee rides in an upright (13° seat-back angle) seat with feet on the floor, and no anti-G suit is worn. The visual end-point is 100% loss of the intensity of the peripheral (green) lights or 50% loss of the intensity of the central (red) lights on the standard centrifuge light bar. All GORS will be terminated at 8.0 G if the visual end-point is not reached sooner, which is unlikely. The RORs begin with a 2.8 G, 15-second exposure, and progress with minimum increments of 0.3 G (3.1 G, 3.4 G, etc.) until the visual end-point is reached during the sustained G exposure and the run is terminated early.

The relaxed RORs measure the hydraulic component of G tolerance, which is determined by vertical heart-to-eye distance, baseline blood pressure, baseline venous capacitance, relative blood volume, and other steady-state circulatory parameters. The GOR 1 and GOR 2 exposures measure the efficacy of the baroreceptor reflexes (principally the carotid sinus reflex) in raising blood pressure in response to G stress. Mean G tolerance for medical evaluees is 4.8 G on the GOR 1 profile and 4.5 G on the GOR 2. Low G tolerance (approximately 1 s. d. below the mean) is 4.1 G on GOR 1 and 3.8 G on GOR 2. Similarly, failure to complete the 3.1 G ROR is indicative of low G tolerance. Typically, relaxed GOR tolerance is approximately 1 G higher than relaxed ROR tolerance, which difference indicates normally responsive baroreflexes. The purpose of the GORS G exposure is to give the evaluee the opportunity to perform his/her anti-G straining maneuver in a progressively more demanding G environment and to precipitate such cardiac dysrhythmias as the evaluee may have a propensity to produce under stressful conditions. We expect evaluees with minimal proficiency in performing the L-1 straining maneuver to add at least 1 G to their relaxed GOR G tolerance when they attempt the GORS profile.

In addition to the GOR 1, RORs, GOR 2, and GORS profiles described above, the Standard Medeval Profiles include rapid-onset runs with straining (RORSs), also called Standard

c. Training Profiles:

1) A 3-G, 15-second, warm-up run

2) A 5-G, 30-second run for practicing the anti-G straining maneuver in a relatively unchallenging G environment

3) A 6 or 7-G, 15-second practice run (optional)

4) An 7.5-G, 15-second training goal/G-tolerance standard

All of the Standard Training Profiles are accomplished with the evaluee sitting in the upright seat, with feet on simulated rudder pedals (F-15 configuration) and wearing a functioning anti-G suit. The Standard Training Profiles are used to assess an aircrew member's ability to raise blood pressure sufficiently to tolerate the maximum G stress likely to be encountered in air combat. The main components of this ability, in addition to the basic hydraulic and cardiovascular reflex factors, are one's skill in performing the anti-G straining maneuver and

one's muscular strength and anaerobic capacity. Evaluees who cannot complete the 7.5 G, 15-second G exposure without losing consciousness or reaching the visual end-point are considered to have low G tolerance.

If an individual fails to accomplish the required 7.5 Gs for 15 seconds on the first session, the first session will be considered training and the evaluee will be given up to two more sessions to reach the desired goal. If after three attempts the evaluee is still unable to perform to the level of the standard, only a categorical (non-high performance) waiver can be considered.

9. **Re-evaluations:** Annual re-evaluation will include the evaluation delineated above with the exception of ; history and physical will be replaced with an interval history and certrifuge medical evaluation is not required.

10. **ACS Waiver Recommendations:** It is impossible to define all the criteria for waivers because of the large combinations of possible results. Therefore, this evaluation plan will use the existing ACS, HQ AFMOA/SGPA approved, standard clinical decision system used for any other flyer referred to the USAF Aeromedical Consultation Service in which the degree of abnormality, the reproducibility, and the confirmation from related exams are all considered in determining if the evaluee would be a risk to flying safety, mission completion, or his own health relative to the average flyer who has not been examined at Brooks AFB.

Clinical Sciences Division Quality Assurance Committee Review

Chairperson,Clinical Sciences Division Quality Assurance Committee

Chief, Clinical Sciences Division

Attachments: **(NOT INCLUDED IN INTERIM REPORT)**
1. Standard Medical Evaluation G Profiles
2. Medical Evaluation Acceleration Consent Form
3. Exercise Treadmill Consent Form