NANYANG TECHNOLOGICAL UNIVERSITY

SEMESTER 2 EXAMINATION 2022-2023

MH4512 – CLINICAL TRIALS

April 2023 Time Allowed: 2 hours

INSTRUCTIONS TO CANDIDATES

1. This examination paper contains **FIVE (5)** questions and comprises **TEN (10)** printed pages.

2. Answer **ALL** questions. The marks for each question are indicated at the beginning of each question.

3. Answer each question beginning on a **FRESH** page of the answer book.

4. This is a **RESTRICTED OPEN BOOK** exam. You are only allowed to bring in **ONE DOUBLE-SIDED A4-SIZE REFERENCE SHEET WITH TEXTS HANDWRITTEN OR TYPED ON THE A4 PAPER** (no sticky notes/post-it notes on the reference sheet).

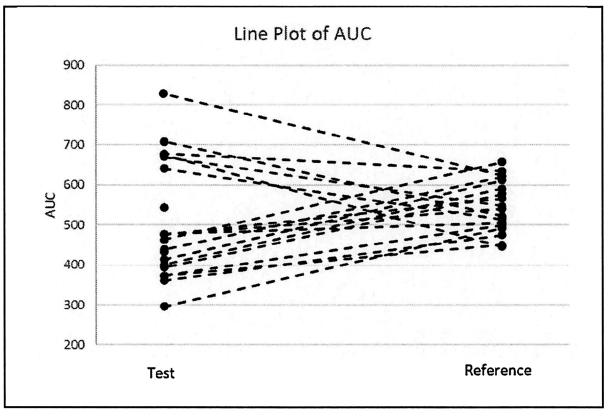
5. Candidates may use calculators. However, they should write down systematically the steps in the workings.

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Question 1. **(25 marks)**

In a clinical trial to compare two formulations of a certain drug, a 2x2 block design was conducted with 20 healthy subjects. Eighteen subjects completed both periods of the trial, 2 dropouts after the first period. The area under the concentration-time curve (AUC) was computed using standard pharmacokinetics technique.

A line plot of the AUC is shown in the figure below.



Two mixed effects models were fitted to the data with ln(AUC) as dependent variable, Formulation (Treat), Period and Sequence (Seqn) as fixed effects, and Subject as random effect. The SAS® codes are given as follows:

```
Title " Model 1: Random";
proc mixed data=one Method=REML noitprint noclprint
noinfo;
 Class Subject Treat Period Seqn;
 Model LnAUC = Treat Period Seqn / DDFM=KR;
 Random Subject;
 Lsmeans Treat / Diff CL alpha=0.10;
Run;
```

```
Title "Model 2: Random + Repeated";
proc mixed data=one Method=REML noitprint noclprint
noinfo;
 Class Subject Treat Period Seqn;
 Model LnAUC = Treat Period Seqn / DDFM=KR;
 Random Subject;
 Repeated / group=Treat;
 Lsmeans Treat / Diff CL alpha=0.10;
Run;
```

(Note: Question No. 1 continues on page 3)

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The attached tables, in the following two pages, show part of the output from the SAS® program after fitting the dataset to the above mentioned models. Use the information from the output to answer the following questions.

a) Explain why a paired t-test is not suitable for this dataset.
b) What are the estimated covariance matrices for the first subject in the trial, based on Model 1 and Model 2?
c) Based on the line plot above, which model do you think is a better fit for the data? Justify your selection.
d) Conduct a likelihood ratio test to determine the better model, at 5% level of significance. (We may assume that $Pr(\chi_1^2 \geq 3.84) = 0.05$).
e) Based on Model 2, estimate the ratio of geometric means for the Test and Reference formulations, with a 90% confidence interval.
f) Based on Model 2, compute the total-subject coefficients of variation (CV%) for the 2 formulations.

(Note: Question No. 1 continues on page 4)

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Model 1: Random
The Mixed Procedure

Number of Observations	
Number of Observations Read	40
Number of Observations Used	38
Number of Observations Not Used	2

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	0.57444404	
1	2	0.41909736	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
Subject	0.004351
Residual	0.03953

Fit Statistics

-2 Res Log Likelihood	0.4
AIC (Smaller is Better)	4.4
AICC (Smaller is Better)	4.8
BIC (Smaller is Better)	6.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treat	1	17.1	2.96	0.1035
Period	1	17.1	1.28	0.2727
Seqn	1	17.4	2.83	0.1105

Least Squares Means

Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.3006	0.04965	33.8	126.89	<.0001	0.1	6.2167	6.3846
Treat	Test	6.1889	0.04684	33.7	132.13	<.0001	0.1	6.1097	6.2681

Differences of Least Squares Means

Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.1118	0.06499	17.1	1.72	0.1035	0.1	-0.00126	0.2248

(Note: Question No. 1 continues on page 5)

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Model 2: Random + Repeated
The Mixed Procedure

Number of Observations	
Number of Observations Read	40
Number of Observations Used	38
Number of Observations Not Used	2

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	0.57444404	
1	2	-9.04708423	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Subject		0.004127
Residual	Treat Reference	0.01033
Residual	Treat Test	0.06588

Fit Statistics	
-2 Res Log Likelihood	-9.0
AIC (Smaller is Better)	-3.0
AICC (Smaller is Better)	-2.2
BIC (Smaller is Better)	-0.1

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Treat	1	18	3.20	0.0902
Period	1	18	1.36	0.2594
Seqn	1	18	3.10	0.0953

Least Squares Means

Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.3007	0.02848	16.1	221.21	<.0001	0.1	6.2510	6.3504
Treat	Test	6.1889	0.05917	18	104.60	<.0001	0.1	6.0863	6.2915

Differences of Least Squares Means

Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.1118	0.06244	18	1.79	0.0902	0.1	0.003516	0.2200

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Question 2. **(20 marks)**

A phase 2, randomized, open-label study was conducted, with the change in body weight (in kg) from baseline to 3 months (BW_chg = 3 months - baseline) as the main clinical outcome. The primary objective was to show non-inferiority of an investigational diet (Test) to a reference diet (Ref). The study used a 3 arms parallel design, the Test, the Reference, and an exercise only program (Control) in overweight patients. Assume that the weight change was normally distributed, a SAS procedure was adopted, and part of the output are presented below. Based on this output answer the following questions.

a) Is there sufficient evidence to conclude that the Test is superior to the Control?
b) Is there sufficient evidence to conclude that the Test is not inferior to the Reference, with a non-inferior margin of 2.0 kg?

For each test above, state clearly your null and alternative hypotheses, the size of your test (α), your decision rules, and your conclusion.

Mixed Effects Model for Body Weight Change
The Mixed Procedure

Number of Observations	
Number of Observations Read	144
Number of Observations Used	144
Number of Observations Not Used	0

Iteration History

Iteration	Evaluations	-2 Res Log Like	Criterion
0	1	598.80593895	
1	1	596.92195180	0.00000000

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Group	Estimate
Residual	Treat Control	4.5487
Residual	Treat Ref	3.0465
Residual	Treat Test	3.7095

(Note: Question No. 2 continues on page 7)

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Fit Statistics	
-2 Res Log Likelihood	596.9
AIC (Smaller is Better)	602.9
AICC (Smaller is Better)	603.1
BIC (Smaller is Better)	611.8

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
2	1.88	0.3898

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
Treat	2	92.7	52.41	<.0001

Least Squares Means									
Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Control	-1.1760	0.3078	47	-3.82	0.0004	0.1	-1.6926	-0.6595
Treat	Ref	-5.1810	0.2519	47	-20.57	<.0001	0.1	-5.6038	-4.7583
Treat	Test	-2.8785	0.2780	47	-10.35	<.0001	0.1	-3.3450	-2.4121

Differences of Least Squares Means										
Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Control	Ref	4.0050	0.3978	90.5	10.07	<.0001	0.1	3.3439	4.6661
Treat	Control	Test	1.7025	0.4148	93	4.10	<.0001	0.1	1.0134	2.3916
Treat	Ref	Test	-2.3025	0.3752	93.1	-6.14	<.0001	0.1	-2.9258	-1.6792

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Question 3. **(20 marks)**

The dose proportionality property of a certain drug developed for patients with hypercholesterolemia was highly desirable. An early phase clinical trial was conducted at several dose levels to evaluate the maximum exposure (Cmax) of the drug as a function of dose. Using a crossover design, eighteen (18) subjects were administered single dose of the drug at dose levels ranging from 3mg to 57mg.

Based on previous experience, a power model was deemed appropriate for the dataset collected from this study. It was also assumed that there were no period or sequence effects. Hence, the following power model was fitted to the data:

$$\ln(Cmax_{ij}) = \beta_0 + \beta_1 \times \ln(Dose_{ij}) + \varphi_i + \varepsilon_{ij},$$

for the j-th observation of Cmax in the i-th subject, with φ_i as the random subject effects.

From a SAS Proc Mixed model, the estimate for β_1 was 1.053 with a 90% confidence interval of (1.037, 1.069).

a) Explain how you would test for dose-proportionality in this setting. State clearly your null and alternative hypotheses, the size of your test (α), and your decision rules. You may use (0.8, 1.25) as the reference interval.
b) Determine the estimated ratio of the dose normalised geometric means of Cmax in the tested dose range, with its 90% confidence interval.
c) Would you be able to conclude dose proportionality of Cmax for the drug used in this trial, over the range of 3mg to 57mg? Justify your answer.
d) Assume that dose extrapolation is allowed, determine the maximum dose ratio where dose proportionality could be declared.
e) What is the minimum dose ratio that a non-proportionate conclusion could be made?

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Question 4. **(20 marks)**

A pharmaceutical company is developing an anti-hypercholesterolemia drug for patients with elevated low-density lipoprotein cholesterol (LDL-C). It is believed that this new anti-hypercholesterolemia drug (Test) is as effective as a currently marketed anti-hypercholesterolemia drug (Control) but has a much better safety profile.

a) A Phase 2 double-blind, randomized, parallel groups design trial is planned with the primary objective of showing non-inferiority of Test to Control. To collect sufficient data on patients treated with the new anti-hypercholesterolemia drug, the allocation ratio of 3:1 for Test against Control is proposed. The primary efficacy endpoint is the change in LDL-C level (mg/dL) for each patient. A difference of 15 mg/dL in LDL-C is of clinical importance. The standard deviation is believed to be approximately 22 mg/dL, obtained from previous studies. Determine the sample sizes required for this trial with Type I error = 0.05, and 90% power to declare non-inferiority when the Test drug is 5 mg/dL less effective than the Control drug.

b) To prepare for the launch of this new anti-hypercholesterolemia drug, a new formulation of the drug is required. Hence, another trial is planned to compare the pharmacokinetics of the new formulation (New) to the formulation currently under development (Reference). Consider a randomized 2x4 crossover trial with the objective to show equivalence in AUC (Area Under the Concentration-time Curve) for this anti-hypercholesterolemia drug with the equivalence margin of (0.8, 1.25), using the two 1-sided test with $\alpha = 0.05$. Determine the number of subjects required to have an 80% power, when the ratio of geometric means is expected to have a 3% difference. The intra-subject CV of the AUC is estimated to be 27% from earlier studies.

(You may assume the following values for the standard normal upper quantiles: $z_{0.025} = 1.960, z_{0.05} = 1.645, z_{0.10} = 1.282, z_{0.20} = 0.842$)

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Question 5. **(15 marks)**

In the development of a new injection device, a pilot study was conducted with 10 subjects to assess the pain level of the new device (New) compared with the conventional device (Reference). In a randomized crossover trial, the subjects were asked to rate their pain upon an injection on a scale of 0 to 10, (0 being no pain and 10 being severe pain).

The following table recorded the pain score.

Subject	101	102	103	104	105	106	107	108	109	110
New	4.9	5.5	6.8	5.3	5.9	6.1	5.1	6.1	6.3	5.6
Reference	5.2	6.5	7.6	5.9	6.3	6.8	4.9	6.2	5.8	6.5

Compute the t-statistic in the Wilcoxon signed rank test, and use the normal approximation approach, with $\alpha = 0.05$, to determine whether the median of the difference in pain score for the new and the reference devices is zero.

State clearly your null and alternative hypotheses, the size of your test, and your decision rules.

(You may assume the following values for the standard normal upper quantiles: $z_{0.025} = 1.960$, $z_{0.05} = 1.645$, $z_{0.10} = 1.282$, $z_{0.20} = 0.842$)

END OF PAPER

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Please read the following instructions carefully:

1. **Please do not turn over the question paper until you are told to do so. Disciplinary action may be taken against you if you do so.**

2. You are not allowed to leave the examination hall unless accompanied by an invigilator. You may raise your hand if you need to communicate with the invigilator.

3. Please write your Matriculation Number on the front of the answer book.

4. Please indicate clearly in the answer book (at the appropriate place) if you are continuing the answer to a question elsewhere in the book.

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