NANYANG TECHNOLOGICAL UNIVERSITY

SEMESTER II EXAMINATION 2024-2025

MH4512 – CLINICAL TRIALS

Apr/May 2025 Time Allowed: 2 hours

INSTRUCTIONS TO CANDIDATES

1. This examination paper contains **FOUR (4)** questions and comprises **NINE (9)** 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 into the examination hall **ONE DOUBLE-SIDED A4-SIZE REFERENCE SHEET WITH TEXTS HANDWRITTEN OR TYPED ON THE A4 PAPER WITHOUT ANY ATTACHMENTS** (e.g. sticky notes, post-it notes, gluing or stapling of additional papers).

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 establish the equivalence between 2 injection methods (using different needles) of a certain drug, a 2-sequence replicate design (TTRR and RRTT) was conducted with 20 healthy subjects. The 2 methods were named Test and Reference. Blood samples were collected at pre-dose and at various times after dosing up through 24 hours post-dose. The area under the concentration-time curve (AUC) of the drug was computed using standard pharmacokinetics technique.

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 and relevant outputs are given as follows:

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

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

(a) State clearly the null and alternative hypotheses, and the decision rules you would use to test for the equivalence of AUC for the Test to Reference methods. You may use the equivalence limits of 0.8 and 1.25, for the ratio of geometric means.

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

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(b) What are the estimated covariance matrices for the first subject in the trial, based on Model 1 and Model 2?

(c) Conduct a log-likelihood ratio test to determine the better model, at 10% level of significance. (We may use $\Pr(\chi_2^2 \geq 4.61) = \Pr(\chi_3^2 \geq 6.25) = 0.10$).

(d) Based on Model 2, estimate the geometric means for the Test and Reference methods, with a 90% confidence interval.

(e) Based on Model 2, estimate the ratio of geometric means for the Test and Reference methods, with a 90% confidence interval. Would you conclude the equivalence in AUC of the Test and Reference methods? Justify your answer.

(f) Based on Model 2, compute the total-subject coefficients of variation (CV%) for the 2 methods.

Model 1: Random Subject Subject*Treat
The Mixed Procedure

Covariance Parameter Estimates	
Cov Parm	**Estimate**
Subject	0.01228
Treat*Subject	0.01140
Residual	0.03007

Fit Statistics	
-2 Res Log Likelihood	1.4
AIC (Smaller is Better)	7.4
AICC (Smaller is Better)	7.8
BIC (Smaller is Better)	10.4

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

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Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Seqn	1	18.1	4.26	0.0535
Treat	1	16.9	2.89	0.1075
Period	3	36.9	1.38	0.2642

Least Squares Means

Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.0688	0.04434	32.5	136.87	<.0001	0.1	5.9938	6.1439
Treat	Test	5.9792	0.04520	32.3	132.29	<.0001	0.1	5.9027	6.0557

Differences of Least Squares Means

Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.08964	0.05274	16.9	1.70	0.1075	0.1	-0.00213	0.1814

Model 2: Random+Repeated

The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Subject	Group	Estimate
UN(1,1)	Subject		0.04072
UN(2,1)	Subject		0.01193
UN(2,2)	Subject		0.006057
Residual		Treat Reference	0.01811
Residual		Treat Test	0.04190

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

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Fit Statistics	
-2 Res Log Likelihood	-3.4
AIC (Smaller is Better)	6.6
AICC (Smaller is Better)	7.5
BIC (Smaller is Better)	11.5

Null Model Likelihood Ratio Test		
DF	Chi-Square	Pr > ChiSq
4	14.50	0.0059

Type 3 Tests of Fixed Effects				
Effect	Num DF	Den DF	F Value	Pr > F
Seqn	1	18.2	4.44	0.0493
Treat	1	17.4	2.83	0.1101
Period	3	33.9	1.68	0.1894

Least Squares Means									
Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.0680	0.05011	18.2	121.10	<.0001	0.1	5.9812	6.1549
Treat	Test	5.9798	0.03775	17.3	158.39	<.0001	0.1	5.9142	6.0454

Differences of Least Squares Means										
Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.08819	0.05238	17.4	1.68	0.1101	0.1	-0.00281	0.1792

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Question 2. **(25 marks)**

A cognitive test checks for problems with patient mental functioning (cognition). The test involves answering basic questions and performing simple tasks. The results of the test can be summarised and converted in a standardized score.

Two independent samples of improvement in the cognitive test score (D-Score) were obtained from a pilot clinical study under 2 different treatment regimens (Test and Reference).

Reference:					
Subject	101	103	106	108	109
D-score	3.2	4.5	3.6	5.3	4.9
Test:					
Subject	102	104	105	107	110
D-score	4.2	6.5	7.6	5.9	6.3

(a) Compute the t-statistic in the Wilcoxon Rank Sum test, and use the normal approximation approach, with $\alpha = 0.05$, to determine whether the median of the D-score for the test and the reference regimens is different. State clearly your null and alternative hypotheses, the size of your test, and your decision rules.

(b) use a non-parametric method to estimate the difference (Test-Reference) of the medians for the two regimens with an approximate 90% confidence interval.

(You may assume the following values for the standard normal upper quantiles: $z_{0.025} = 1.960$, $z_{0.05} = 1.645$, $z_{0.10} = 1.282$, $z_{0.20} = 0.842$; and, $k = 5$ for the calculation of a 90% confidence interval for sample sizes $n_1 = n_2 = 5$, based on the Wilcoxon rank sum distribution.)

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Question 3. **(25 marks)**

An early phase clinical trial was conducted at several dose levels to investigate the dose proportionality property of a certain drug developed for patients who need to control their blood pressure. In the study, a crossover design with twelve (12) subjects were administered single dose of the drug at dose levels ranging from 3 mg to 90 mg. The area under the concentration-time curve (AUC) of the drug was evaluated as a function of dose.

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:

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

for the j-th observation of AUC in the i-th subject, with φ_i as the random subject effects. The following table summarises the estimates and their 90% confidence intervals for the random and fixed effects. Use the information in the table to answer the following questions.

Mixed Effects Model for DP of LnAUC

The Mixed Procedure

Convergence criteria met.

Covariance Parameter Estimates

Cov Parm	Estimate
Subject	0.06798
Residual	0.07717

Solution for Fixed Effects

Effect	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Intercept	0.8898	0.1307	38.6	6.81	<.0001	0.1	0.6696	1.1100
LnDose	1.0505	0.03533	35	29.74	<.0001	0.1	0.9908	1.1102

(Note: Question No. 3 continues on page 8)

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(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 AUC in the tested dose range, with its 90% confidence interval.

(c) Would you be able to conclude dose proportionality of AUC for the drug used in this trial, over the range of 3mg to 90mg? Justify your answer.

(d) Determine whether the dose proportionality could be declared within a 10-fold range of the dose.

(e) Suppose in another study of the same drug, the estimate for β_1 was 1.0505 with a 90% confidence interval of (1.0105, 1.0905). Determine the maximum dose ratio where dose proportionality could be declared.

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Question 4. **(25 marks)**

A pharmaceutical company is developing a drug for patients with insufficiently controlled type 2 diabetes mellitus. It is believed that this new drug (Test) is much more effective than a currently marketed drug (Control).

(a) A Phase 2 double-blind, randomized, parallel groups design trial is planned with the primary objective of showing superiority of Test over Control. To collect sufficient data on patients treated with the new drug, the allocation ratio of 2:1 for Test against Control is proposed. The primary efficacy endpoint is the change in Haemoglobin A1C (HbA1c) for each patient. The standard deviation of HbA1c is believed to be approximately 3%, obtained from previous studies. Determine the sample sizes required for this trial with Type I error = 0.05, and 90% power to declare superiority when the Test drug is 1.5% more effective than the Control drug.

(b) In Part (a), if the pharmaceutical company decides to use 74 and 37 subjects for the Test and the Control drugs, respectively, for the Phase 2 trial, what would be the approximate power of the trial?

(c) To prepare for the launch of this new 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 2x2 crossover trial with the objective to show equivalence in AUC (Area Under the Concentration-time Curve) for this new 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 90% power, when the ratio of geometric means is expected to have a 5% difference. The intra-subject CV of the AUC is estimated to be 30% from earlier studies.

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

END OF PAPER

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MH4512 CLINICAL TRIALS

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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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