NANYANG TECHNOLOGICAL UNIVERSITY

SEMESTER II EXAMINATION 2023-2024

MH4512 – CLINICAL TRIALS

May 2024 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 oral formulations of a certain drug, a 2-sequence replicate design (TTRR and RRTT) was conducted with 20 healthy subjects. The 2 formulations were: Test = five 100mg tablets and Reference = 20 mL of a suspension. Blood samples were collected at pre-dose and at various times after dosing up through 24 hours post-dose. The maximum drug concentration (Cmax) from the concentration-time curve was computed using standard pharmacokinetics technique.

Two mixed effects models were fitted to the data with ln(Cmax) 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+Repeated";
proc mixed data=one Method=REML noitprint noclprint noinfo;
 Class Period Treat Seqn Subject;
 Model LnCmax = Seqn Treat Period / DDFM=KR;
 Random Treat /TYPE=UN Subject=SUBJECT;
 Repeated / Group=Treat;
 Lsmeans Treat / Diff CL alpha=0.10;
Run;
```

```
Title " Model 2: Simple Random";
proc mixed data=one Method=REML noitprint noclprint noinfo;
 Class Period Treat Seqn Subject;
 Model LnCmax = Seqn Treat Period / DDFM=KR;
 Random Subject;
 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 Cmax for the Test to Reference formulations. You may use the equivalence limits of 0.8 and 1.25, for the ratio of geometric means.

(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 $\Pr(\chi_3^2 \geq 6.25) = 0.10$).

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

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(d) Based on Model 1, estimate the geometric means for the Test and Reference formulations, with a 90% confidence interval.

(e) Based on Model 1, estimate the ratio of geometric means for the Test and Reference formulations, with a 90% confidence interval. Would you conclude the equivalence in Cmax of the Test and Reference formulations? Justify your answer.

(f) Based on Model 1, compute the inter-, intra- and total-subject coefficients of variation (CV%) for the 2 formulations.

Model 1: Random+Repeated
The Mixed Procedure

Covariance Parameter Estimates			
Cov Parm	**Subject**	**Group**	**Estimate**
UN(1,1)	Subject		0.04656
UN(2,1)	Subject		0.01212
UN(2,2)	Subject		0.006384
Residual		Treat Reference	0.02060
Residual		Treat Test	0.04120

Fit Statistics	
-2 Res Log Likelihood	1.1
AIC (Smaller is Better)	11.1
AICC (Smaller is Better)	12.0
BIC (Smaller is Better)	16.1

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Seqn	1	18.3	3.71	0.0698
Treat	1	17.6	1.44	0.2454
Period	3	35	1.48	0.2377

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

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Least Squares Means

Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.0471	0.05356	18.2	112.91	<.0001	0.1	5.9543	6.1399
Treat	Test	5.9804	0.03775	17.3	158.43	<.0001	0.1	5.9148	6.0460

Differences of Least Squares Means

Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.06671	0.05551	17.6	1.20	0.2454	0.1	-0.02966	0.1631

Model 2: Simple Random
The Mixed Procedure

Covariance Parameter Estimates

Cov Parm	Estimate
Subject	0.01765
Residual	0.03997

Fit Statistics

-2 Res Log Likelihood	8.4
AIC (Smaller is Better)	12.4
AICC (Smaller is Better)	12.6
BIC (Smaller is Better)	14.4

Type 3 Tests of Fixed Effects

Effect	Num DF	Den DF	F Value	Pr > F
Seqn	1	18.2	3.38	0.0825
Treat	1	54.7	2.41	0.1260
Period	3	53.9	2.03	0.1202

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

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Least Squares Means

Effect	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	6.0503	0.04375	32.1	138.28	<.0001	0.1	5.9762	6.1244
Treat	Test	5.9788	0.04436	32.8	134.78	<.0001	0.1	5.9037	6.0539

Differences of Least Squares Means

Effect	Treat	Treat	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Treat	Reference	Test	0.07150	0.04602	54.7	1.55	0.1260	0.1	-0.00550	0.1485

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Question 2. **(25 marks)**

The visual analogue scale (VAS) is a simple and frequently used method for the assessment of variations in intensity of pain. 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 scores.

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	5.1	6.0	7.6	5.9	5.8	6.8	4.8	6.5	5.8	6.5

(a) 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.

(b) Suppose a mixed effects model was fitted with the pain score as dependent variable, device as fixed effect and subject as random effect. A SAS procedure was adopted, and part of the output are presented below. Based on this output, is there sufficient evidence to conclude that the New device is superior to the Reference in terms of pain score? State clearly your null and alternative hypotheses, the size of your test (α), your decision rules, and your conclusion.

(c) Comment on the difference between the two tests in Parts (a) and (b). What are the assumptions needed for each test? Which test do you prefer?

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

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

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```
* Analysis for Pain Score  ********;
Title2 "Analysis for Pain Score";
proc mixed data=one Method=REML noitprint noclprint noinfo;
  Class Device Subject;
  Model Score = Device / DDFM=KR ;
  Random Subject ;
  Lsmeans Device / Diff CL alpha=0.05;
Run;
```

Analysis for Pain Score
The Mixed Procedure

Covariance Parameter Estimates	
Cov Parm	**Estimate**
Subject	0.3891
Residual	0.1153

Fit Statistics	
-2 Res Log Likelihood	35.2
AIC (Smaller is Better)	39.2
AICC (Smaller is Better)	40.0
BIC (Smaller is Better)	39.8

Type 3 Tests of Fixed Effects				
Effect	**Num DF**	**Den DF**	**F Value**	**Pr > F**
Device	1	9	4.44	0.0644

Least Squares Means									
Effect	Device	Estimate	Standard Error	DF	t Value	Pr > |t|	Alpha	Lower	Upper
Device	New	5.7600	0.2246	11.3	25.65	<.0001	0.1	5.3576	6.1624
Device	Reference	6.0800	0.2246	11.3	27.07	<.0001	0.1	5.6776	6.4824

Differences of Least Squares Means										
Effect	**Device**	**Device**	**Estimate**	**Standard Error**	**DF**	**t Value**	**Pr > |t|**	**Alpha**	**Lower**	**Upper**
Device	New	Reference	-0.3200	0.1519	9	-2.11	0.0644	0.1	-0.5984	0.04159

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Question 3. **(25 marks)**

The dose proportionality property within a 5-fold range of a certain drug developed for patients who need to control their body weight was highly desirable. An early phase clinical trial was conducted at several dose levels to evaluate the area under the concentration-time curve (AUC) 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 5mg to 50mg.

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.

From a SAS Proc Mixed model, the estimate for β_1 was 1.153 with a 90% confidence interval of (1.0537, 1.253).

(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 5mg to 50mg? Justify your answer.

(d) Determine whether the dose proportionality could be declared within the desirable 5-fold range of the dose.

(e) Suppose in another study of the same drug, the estimate for β_1 was 1.024 with a 90% confidence interval of (0.970, 1.114). 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 weight loss drug for patients with high body mass index (BMI). It is believed that this new weight loss drug (Test) is much more effective than a currently marketed weight loss 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 3:1 for Test against Control is proposed. The primary efficacy endpoint is the change in body weight for each patient. The standard deviation of weight change is believed to be approximately 34 kg, 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 18 kg more effective than the Control drug.

(b) To prepare for the launch of this new weight loss 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 weight loss 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

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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