Overview Answers

Keine Garantie für Vollständigkeit oder Richtigkeit

1. **Study Design and Bias**

   1. On study designs we got
      1. parallel design
      2. Cross Over Design
      3. Faktorial Design

      Their main features are
      1. looking at progression of disease/disorder, no carryover effects, issue Variability in response occurring within the same patient
      2. statistically efficient, confounding covariates effects are reduced, several bias as well
      3. studying effect of certain value by using combinations
   2. Problems influencing outcome/interpretation of data when conducting clinical trial are different forms of bias(selection attrition detection ascertainment confounding) selection means eg non selective population so not randomized(external)

      - attrition means loosing track of patients
      - detection means wrong measurement method
      - ascertainment eg non selective population so not randomized(internal)
      - confounding means relating unrelated things

      ! Procedure to reduce/prevent certain forms of bias is 1.randomization 2. controlling

      ! Thereby removing with 1 selection and concealment bias and with 2 Ascertainment and Performance Bias

2. **Diagnostic Tests**

   1. Definition of important medical terms used in diagnostic tests

      1. gold standard means best performing test available
      2. prevalence/Prävalenz $Pr = P(K^+) = \frac{\text{Number of people suffering illness}}{\text{size of people}}$ and independent of test decision
      3. sensitivity/Sensivität $Se = P(T^+|K^+) = \frac{\text{Number of diseased patients with positive test}}{\text{Number of diseased patients}}$ number of true positive cases correctly identified, prob. of positive test within diseased population
      4. specificity/Spezifität $Sp = P(T^-|K^-) = \frac{\text{Number of healty patients with negative test result}}{\text{Number of healthy people}}$ number of true negative cases correctly identified by test, prob. of negative test result within diseased population
      5. cut-off directly influences Specificity and Sensitivity, a good ratio has to be found with respect to clinical reasons, at or near shoulder of curve and according to Youden Index (Y=Se+Sp-1), dot plot might help to identify, otherwise ROC-Curve helps
      6. predictive values are
         A. PPV pos.pred.value $PV^+ = P(K^+|T^+) = \frac{\text{healthy persons with pos Test}}{\text{Persons with pos Test}} = \frac{\text{Se}\times\text{Pre}}{\text{Se}\times(\text{Pre})+(1-\text{Sp})\times(1-\text{Pre})}$
         B. NPV neg.pred.value $PV^- = P(K^-|T^-) = \frac{\text{healthy persons with neg Test}}{\text{Persons with neg Test}} = \frac{\text{Sp}\times(1-\text{Pre})}{\text{Sp}\times(1-\text{Pre})+(1-\text{Se}\times\text{Pre})}$
         C. Bayes theorem $P(A|B) = \frac{P(B|A)*P(A)}{P(B)}$
      7. odds a-priori odds $\frac{\text{Prevalence}}{1-\text{Prevalence}}$, a-postiori $\frac{PV^+}{1-PV^+}$
      8. likelihood ratio LR defines usefulness of test
         - $LR^+ = \frac{Se}{1-Sp}$

- $LR^- = \frac{1-Se}{Sp}$
- Accetable:$LR^+ > 3, LR^- < 0.3$,excellent:$LR^+ > 10, LR^- < 0.1$
- higher LR^+ of test, but not if its a good indicator(depends on prevalence)

2. Which of previously mentioned values are influenced by test decision? We can decide our significance level and the appriorate test to choose in relation to the study who was evaluated. Depending on the data we can additionally choose a cut-off value
3. How does a cut-off relates to that if high value → illness? Cut-off only is an indicator for Sens and Spec on data, but can not change Prevalence and statistically significance for all the biases
4. Quality of diagnostic tests can be evaluated by LR^+, LR^- and prevalence
5. Illustration of cut-off on test decision and how to choose appropriate cut-off
   Checking for AUC by Youden Index we can approximate a cut off value, this means we evaluate approximately for all Spec and Sens the given data finding an optimum looking at costs for false tests as well
6. How does decision rule influence sensitivity and specificity of combined test if conducted in serial or parallel manner? Serial for examination whenever fast judgement not needed, parallel conduct on fast judgment is needed Depending on statistically independency the probabilities can be calculated as well as Spec and Sens

3. **Confidence Intervals**

   MasterFormula
   (normal dist.) CI (unknown variance)
   $\left[\bar{x} - t_{(1-\frac{\alpha}{2};n-1)}SEM \ ; \ \bar{x} + t_{(1-\frac{\alpha}{2};n-1)}SEM\right]$
   standard error of the mean (SEM) $SE_{\bar{x}} = \frac{s_x}{\sqrt{n}}$ where s_x ist STD
   $n > 30$ or variance σ^2 known → using standardised normal distribution for t

   1. CI one-sided continuous parameter(normal dist.) using MasterFormula except with doubling α since we know there are only values between 0 and 100 %
   2. CI two-sided continuous parameter(normal dist.) using MasterFormula
   3. difference of parameters between 2 unpaired groups
      $\left[\bar{x_1} - \bar{x_2} - SE_{diff} * t_{(1-\frac{\alpha}{2};n_1+n_2-1)} \ ; \ \bar{x_1} - \bar{x_2} + SE_{diff} * t_{(1-\frac{\alpha}{2};n_1+n_2-1)}\right]$
      $SE_{diff} = \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}\sqrt{\frac{(n_1-1){s_{x_1}}^2+(n_2-1){s_{x_2}}^2}{n_1+n_2-2}}$
   4. exact/approximate unpaired CI for proportions with χ^2-Test $p_{1,2} = \frac{m_1}{n_1} - \frac{m_2}{n_2} \pm z_{1-\frac{\alpha}{2}}\sqrt{\frac{\frac{m_1}{n_1}(1-\frac{m_1}{n_1})}{n_1} + \frac{\frac{m_2}{n_2}(1-\frac{m_2}{n_2})}{n_2}}$
      m number of positive tests, n total test number or imagining abcd table with illness above:
      $T = n * \frac{(ad-bc)^2}{(a+b)(a+c)(b+d)(c+d)}$
   5. exact/approximate paired CI for proportions $p_{1,2} = \frac{m}{n} \pm z_{1-\frac{\alpha}{2}}\sqrt{\frac{\frac{m}{n}(1-\frac{m}{n})}{n}}$ m number of positive tests, n total test number
   6. approximate paired CI for frequence $\bar{d} \pm \frac{s}{\sqrt{n}} * t_{n-1,1-\frac{\alpha}{2}}$
   7. quantil tables checking

4. **Statistical Tests**

   1. Test to use — Procedure — Formula

Condition For Binom, t-Test and Chi-Test
Stating H_0 first(usually some equality of values), we calculate p-Value by formula and check under H_0 (0-hypothesis) if the appropriate t/χ/binom value is ≥ 0.05 or whatever significance level is given. If yes, we reject, otherwise we can assume H_0 is true, the opposite goes for type 2 error β which has to be $\leq$ significance value for H_1 to be false

1. Binomial Test — only 2 events, calculation of possibilities due to hypothesis — assuming we have binomial distribution we can calculate the CI and check if we are biased or not or the p-Value — $bin(k,n,p) = \binom{n}{k} * p^k * (1-p)^{n-k}$
2. paired t-Test — dependencies between groups — $T = \sqrt{n}\frac{\bar{d}}{s_x}$
3. unpaired t-Test — no dependencies between groups — $T = \frac{|\bar{x_1} - \bar{x_2}|}{s_p * \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$
4. χ^2-test — only for frequencies — $\chi^2_T = \sum_{allCells} \frac{(frq_{obs} - freq_{exp})^2}{freq_{exp}}$
5. ANOVA SEE BELOW
6. Agreemant(Bland-Altmann) we plot mean difference of value and the difference of data points and paint asymptotic $\pm 2 s_d$ line over mean difference, for exact we plot $\frac{s_d}{\pm}\sqrt{n} * t_{n-1,1-\frac{\alpha}{2}}$ lines
7. Agreement(Kappa) Cohens Kappa $\kappa = \frac{p_o - p_e}{1-p_e}$, (zeile,spalte)$p_o = (T^+, K^+) * (T^-, K^-), p_e = (\frac{\sum T^+}{n} * \frac{\sum K^+}{n} + \frac{\sum T^-}{n} * \frac{\sum K^-}{n}), > 0.81 \rightarrow$ very good, $0.61 - 0.8 \rightarrow$ good, $0.41 - 0.6 \rightarrow$ fair, $0.21 - 0.4 \rightarrow$ slight, $< 0.2 \rightarrow$ poor

2. type-1 errors is probability of error occuring on H_0 hypothesis, type-2 errors is probability of error occuring on H_1 hypothesis
3. How can paird/unpaired t-test and χ^2-test be conducted with help of CI ? Yes, checking the CI we can identify for significance. If 0 is including the CI area we know that there is no statistically significance. We can do this for all of the tests

5. **ANOVA**

1. procedure repeating for ANOVA
   1. Calculating Model $SS_A = \sum_{i=1}^{k} n_i(\bar{y_{i\bullet}} - \bar{y_{\bullet\bullet}})^2$
   2. Calculating corrected total $SS_{CT} = \sum_{i,j}(\bar{y_{ij}} - \bar{y_{\bullet\bullet}})^2$
   3. Calculating error $SS_R = SS_{CT} - SS_A$
   4. Calculating Test Statistics $F_0 = \frac{\frac{1}{k-1}SS_A}{\frac{1}{N-k}SS_R}$
   5. Calculating Model Fit(Residual) $R^2 = \frac{SS_A}{SS_{CT}}$ has to be high(close to 1 is good)
2. Analazing residuals we have to consider R^2-Test and F_0-Test to check if our statement is correct
3. Evaluating model fit on ANOVA by SEE ABOVE
4. Considering adjusting the significance level for post-hoc tests, if ANOVA is significant we are doing, because ANOVA does not tell which group was affected and these are trying to do
5. Methods for multiple testing adjustment are Bonferroni and Hochberg method
6. Their features are simpleness and efficency for small test sets for Bonferroni and accuracy and correctness also for large test sets for Hochberg
7. Adjustment is performed by taking into effect that positive test should not lower the p-Value in Hochberg
8. Test decision is performed for the adjusted values by calculating p-Values and afterwards comparing comparing test results via Hochberg or Bonferri where for bigger varity of test one shall use Hochberg

6. **Agreement**

1. Investigating the agreement between 2 methods with contiuous parameters we analyze location and scale shift from expected data to measured data by Bland-Altman Plot visually or by κ for linear correlation
2. In an Bland-Altman plot we need to analyze agreement by calculating the differences and the mean of them as well as expected variance over difference and looking for scale and location shift

3. Difference between Association and Agreement is Agreement means with low error probability the data fit a certain model while association means the correlation or dependency of two data set
4. Relationships and problems taken into account by Lin's Concordance Correlation Coefficient are location and scale shift by using Accuracy on Pearson linear coefficient
5. Lin's CC is evaluated by $\frac{2s_{12}}{s_1^2+s_2^2+(\bar{x_1}-\bar{x_2})^2}$
6. Agreement if parameter is categorical can be measured by calculating the sum over appearance (to sample it to a group) and measure if this was correct
7. Kappa is evaluated by SEE ABOVE
8. For categorical agreement parameter in SE(kappa) we can calculate the corresponding confidence interval by
9. The paradox of Cohen's Kappa means if we have symmetric inbalance we get lower κ, because it distinguishes between agreement of findings in positive and negative ratings

7. **SAS**

1. Mean and standard deviation of a parameter in SAS can be calculated by

```
/*ii) calculate mean and standard deviation for height seperated by sex */
PROC MEANS data=WORK.workingdata MEAN STD;
  VAR HEIGHT;
  BY SEX;
RUN;
```

2. Option for different groups can be added by

```
PROC MEANS DATA=bodyfat MEAN STD MIN MAX CLM;
  VAR bodyfat height weight;
  CLASS gender;
RUN;
```

3. Calculating covariance and (pearson) correlation between two(or more) variables in SAS by

```
/*c pairwise Person and Spearman correlation*/
/*already sorted data by sex*/
PROC CORR data=WORK.workingdata PEARSON SPEARMAN;
  VAR HEIGHT WEIGHT1;
RUN;
```

4. Creating $n \times m$ table in SAS by

```
data Ex11b;
input treatment $ outcome numbers;
datalines;
C 0 7
C 1 3
T 0 2
T 1 8
;
run;
```

5. Procedure to conduct paired/unpaired t-test, χ^2-test and ANOVA

```
/* unpaired t-test SIDES=2 for twosided, h0=value for different hypothesis */
  PROC TTest DATA=bodyfat;
    VAR bodyfat age;
    CLASS gender;
  RUN;
/*PAIRED pulse1*pulse2; for paired t-test*/
/*$Chi-test */
PROC freq data=earinfection;
  tables location*sex / chisq;
RUN;
/* ANOVA */
PROC GLM DATA=WORK.MinutesData;
```

```
  CLASS COUNTRY ;
  MODEL TVTIME = COUNTRY ;
RUN;
```

6. General structure of code to perform corresponding test

```
PROC TESTNAME DATA=DATA_STORE;
  VAR variable_to_test;
  CLASS combined_variables;
  PAIRED pair1*pair2; /*optional*/
RUN;
```

7. How to find corresponding values for the test decision in output
   paired/unpaired t-Test $\rightarrow$ t-Value, checking for significance level next to it
   χ^2-Test $\rightarrow$ standing next to it and looking on p-Value next to it for checking significance level
   ANOVA $\rightarrow$ F-Value checking, probability lower than test and higher next to it, R^2 for model fit

8. Calculating Kappa(Agreement)

```
proc freq data=SkinCondition order=data;
   tables Derm1*Derm2 / agree noprint;
   test kappa;
   weight Count;
run;
```