Statistical analysis plan CAP-PACT trial

06-07-2018

SUMMARY

The primary aim of the CAP-PACT trial is to demonstrate the safety and effectiveness of the antibiotic stewardship intervention to decrease the use of broad-spectrum antibiotics. The study has two co-primary outcomes: effectiveness is determined by broad-spectrum antibiotic use in days of therapy (DOT) and safety is determined by 90-day mortality. The analysis on antibiotic use will be a superiority analysis (to demonstrate a reduction in broad-spectrum antibiotic use) and the analysis on clinical outcome will be a non-inferiority analysis (non-inferiority in 90-day mortality). Three of the twelve hospitals dropped out from the study before the intervention was introduced. Two because the principal investigator left the hospital and no suitable replacement was available, and one because of insufficient patient recruitment. These hospitals will not be included in the data analysis. From the remaining centres, the data analysis will be performed on all patients included from 01-Nov-2015 till 01-Nov-2017, irrespective of the compliance to the stewardship intervention. The detailed statistical analysis plan has been established prior to database lock.

The primary analysis will be performed on patients with a clinical diagnosis of community-acquired pneumonia (CAP), with a sensitivity analysis in patients with radiologically confirmed CAP. Missing data will be handled by multiple imputation. Separate models will be fitted per endpoint. Adjusted models are corrected for the confounders: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment. All models will be mixed effects regression models with a random intercept, a random effect per hospital, and time as a fixed linear effect. All models will be checked for cluster autocorrelation.

The models used for the statistical analysis are as follows:

Co-primary outcomes:

90-day mortality:

All analyses will be performed as mixed effects logistic regression models, both crude and adjusted

- Intention-to-treat (primary analysis):
  - Reported as risk differences as described by Kleinman and Norton (Health Serv Res 2009 Feb;44(1):288-302).
  - Test for non-inferiority: the upper limit of the 90% CI of the estimated absolute risk difference should not be more than 3%.
- As-treated (secondary analysis):

        - Determinant: empirical treatment with narrow-spectrum antibiotics versus broad-spectrum antibiotics
        - Reported as risk differences with corresponding 90% CI and test for non-inferiority (as ITT)
    - Complier Average Causal Effect (CACE) (secondary analysis)
        - As described by Greenland (Int J Epidemiol 2000; 29: 722–9.)
        - Randomisation will be used as an instrumental variable
        - Reported as risk differences with corresponding 90% CI

<u>Broad-spectrum days of therapy (DOT)</u>

Amoxicillin, penicillin and doxycycline are considered narrow-spectrum, other antibiotics are considered broad-spectrum antibiotics. Dual therapy with two broad-spectrum antibiotics will be considered as one broad-spectrum DOT, with a sensitivity analysis considering them as two broad-spectrum DOTs.

- Intention-to-treat (primary analysis):
    - Mixed effects Poisson regression models with broad-spectrum DOTs per patient as outcome

Secondary outcomes:

- 30-day mortality: as with 90-day mortality.
- Length of hospital stay: mixed effects cox regression model with in-hospital mortality as competing endpoint
- ICU admissions: mixed effects logistic regression model
- Readmissions: mixed effects logistic regression model
- Antibiotic switches: proportion estimated with mixed effects logistic regression models, time till switch estimated with mixed effects cox regression models

INTRODUCTION

This document describes the statistical analysis to determine the effect of an antimicrobial stewardship intervention on broad-spectrum antibiotic use and clinical outcome. The primary aim of the CAP-PACT trial is to demonstrate the safety and effectiveness of the antibiotic stewardship intervention to decrease the use of broad-spectrum antibiotics. The CAP-PACT trial is a stepped wedge cluster randomised trial. The implemented stewardship intervention consisted of (1) education, (2) audit and feedback, and (3) motivation of opinion leaders. The study has two co-primary outcomes: effectiveness is determined by broad-spectrum antibiotic use in days of therapy (DOT) and safety is determined by 90-day mortality. The analysis on antibiotic use will be a superiority analysis (to demonstrate a reduction in broad-spectrum antibiotic use) and the analysis on clinical outcome will be a non-inferiority analysis (non-inferiority in 90-day mortality). Three of the twelve hospitals dropped out from the study before the intervention was introduced. Two because the principal investigator left the hospital and no suitable replacement was available, and one because of insufficient patient recruitment. These hospitals will not be included in the data analysis. From the remaining centres, the data analysis will be performed on all patients included from 01-Nov-2015 till 01-Nov-2017, irrespective of the compliance to the stewardship intervention. The primary analysis will be performed on patients with a clinical diagnosis of community-acquired pneumonia (CAP). A sensitivity analysis will be performed in patients with radiologically confirmed CAP. All confounders used on the models are selected based on their theoretic associations with the outcome and will be added to the model without testing their distribution in the baseline and intervention periods.

Missing data, including outcomes, will be imputed by multiple imputation, with the exception of data on respiratory rate, heart rate, and confusion at admission; the values for these variables were assumed to be normal when data were missing. As a sensitivity analysis, a complete case analysis will be performed.

The detailed statistical analysis plan has been established prior to database lock.

OVERVIEW

DESCRIPTIVE STATISTICS

- Inclusion flowchart
- A baseline table comparing patients included in the control period to patients in the intervention period
- Process measures of the stewardship intervention
- Kaplan Meier curves of 90-day survival
- Visual representation of outcomes over time per hospital will be provided as recommended by Haines and Hemming (2018), example:

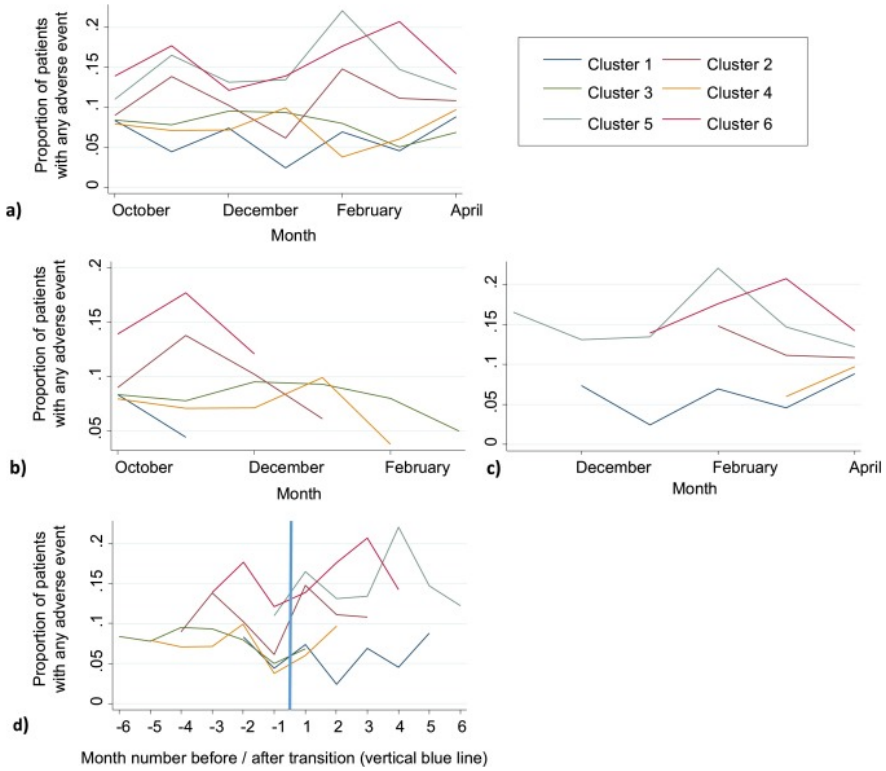

Figure 3

Line graphs based upon: a) whole trial data using calendar time; b) control period data using calendar time; c) intervention period data using calendar time; and d) whole trial data using time relative to the transition period.

Haines TP, Hemming K. Stepped-wedge cluster-randomised trials: level of evidence, feasibility and reporting. J Physiother. 2018 Jan;64(1):63-66. doi: 10.1016/j.jphys.2017.11.008. Epub 2017 Dec 27.

PRIMARY OUTCOMES

Clinical outcome (90-day mortality)

The primary analysis will be conducted according to intention-to-treat (ITT). In addition, we will perform an as-treated (AT) analysis and a Complier Average Causal Effect (CACE) analysis.

1. *Intention-to-treat (ITT) analysis*

In the ITT analysis, patients included in the intervention period will be compared to patient in the control period.

1a. 90-day mortality ITT crude

- Mixed effects logistic regression model, outcome: 90-day all-cause mortality (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Determinant: intervention period versus control period
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- To estimate risk differences from the logistic regression model, we will use a technique described by Kleinman and Norton (Health Serv Res 2009 Feb;44(1):288-302).
- Outcomes will be reported as risk differences with corresponding 90% CI (i.e. a one-sided alpha of 0.05)
- Test for non-inferiority: the upper limit of the 90% CI of the estimated absolute risk difference should not be more than 3%

1b. 90-day mortality ITT adjusted

- As (1a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

2. *As-treated (AT) analysis*

In the AT analysis, patients receiving narrow-spectrum antibiotics (amoxicillin, penicillin, doxycycline) will be compared to patients receiving broad-spectrum antibiotics (all other antibiotics).

2a. 90-day mortality AT crude

- As (1a), with:
- Determinant: empirical treatment with narrow-spectrum antibiotics versus broad-spectrum antibiotics. Empirical treatment is defined as all antibiotic therapy given on the day of admission.
    - Narrow-spectrum antibiotics include:
        - Amoxicillin, penicillin, doxycyclin
    - Broad-spectrum antibiotics include:
        - Regiments including any of the other antibiotics

2b. Mortality AT adjusted

- As (2a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment, and controlled for control/intervention period

3. *Complier Average Causal Effect (CACE) / instrumental variable analysis*

The Complier Average Causal Effect (CACE) analysis can be used to adjust for non-compliance in a randomised controlled trial. In the CACE analysis, the effect of empirical treatment with narrow-spectrum versus broad-spectrum on mortality is estimated if all patients in the group with equipoise (i.e. in patients eligible to be treated with narrow-spectrum or broad-spectrum antibiotics) were empirically treated with narrow-spectrum or broad-spectrum antibiotics, i.e. 100% receiving broad-spectrum antibiotics in the control period and 100% receiving narrow-spectrum antibiotics in the intervention period.

3a. Mortality CACE crude

- As (1a), with:
- Randomisation will be used as an instrumental variable
- CACE analysis will be performed by dividing the ITT effect by the difference in the observed probabilities of receiving narrow-spectrum antibiotics between the two treatment allocation groups, as described by Greenland S. An introduction to instrumental variables for epidemiologists. Int J Epidemiol 2000; 29: 722–9.

- As the study was not designed to be powered for a CACE analysis, outcomes will be reported as risk differences with corresponding 95% CI without a formal non-inferiority analysis

3a. Mortality CACE adjusted

- As (3a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Antibiotic use (days of therapy (DOT))

Antibiotic use will be classified as broad-spectrum and narrow-spectrum median DOTs per patient. We will not standardize the DOT per patient days because the intervention can possibly affect the length of stay on patients. This can be considered a pragmatic effect of the intervention, which we want to measure, and not correct for. The primary outcome will be broad-spectrum DOTs.

Days that patients receive narrow-spectrum antibiotics (amoxicillin, penicillin, doxycycline) are defined as narrow-spectrum DOTs, and days that patients receive broad-spectrum antibiotics (any other antibiotic regimen) are defined as broad-spectrum DOTs. In the primary analysis, dual therapy will be counted one DOT (i.e. patients receiving combination therapy with a narrow-spectrum antibiotic and a broad-spectrum antibiotic will be counted as one broad-spectrum DOT, and patients receiving combination therapy with two broad-spectrum antibiotics will also be counted as one broad-spectrum DOT). In a sensitivity analysis, dual therapy will be counted as two DOTs. Both in-hospital and post-discharge antibiotic use will be included in the analysis of DOTs. Narrow-spectrum DOTs will be analysed similar to broad-spectrum DOTS.

4a. Broad-spectrum DOT, ITT crude

- Mixed effects Poisson regression model, outcome: broad-spectrum DOT (count data)
    - The assumptions for Poisson regression will be checked. In case of over or underdispersion, a negative binomial distribution will be used.
- Random intercept and random effect per hospital
- Time as fixed linear effect
    - As a sensitivity analysis: slope change after intervention will be determined
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as the median difference in broad-spectrum DOT per patient with corresponding 95% confidence intervals

4a. Broad-spectrum DOT, ITT adjusted

- As (4a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

SECONDARY OUTCOMES

30-day mortality

5a. 30-day mortality ITT crude

- As (1a)

5b. 30-day mortality ITT adjusted

- As (1b)

5c. 30-day mortality AT crude

- As (2a)

5d. 30-day mortality AT adjusted

- As (2b)

5e. 30-day mortality CACE crude

- As (3a)

5f. 30-day mortality CACE adjusted

- As (3b)

Length of stay

6a. Length of stay ITT Crude

- Survival analysis model (Fine and Gray), outcome: time to discharge alive
    - Competing endpoint: in-hospital mortality
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC

- Determinant: intervention period versus control period
- Outcomes will be reported as hazard ratio's with corresponding 95% confidence intervals

6b. Length of stay ITT adjusted

- As (6a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

ICU admissions

7a. ICU admissions ITT Crude

- Mixed effects logistic regression model, outcome: ICU admission (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

7b. ICU admissions ITT Adjusted

- As (7a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Readmissions (30-day)

8a. Readmissions ITT Crude

- Mixed effects logistic regression model, outcome: readmissions within 30 days of hospital admission (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC

- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

8b. Readmissions ITT Adjusted

- As (8a), with:
- Adjustment for confounding co-variates: PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

Antibiotic switches

Antibiotic switches will be described as (1) switches from broad-spectrum to narrow-spectrum antibiotics, (2) switches from narrow-spectrum to broad-spectrum antibiotics, (3) switches from intravenous to oral antibiotics, (4) switches from oral to intravenous and intravenous to oral antibiotics. Descriptive statistics will be used to describe the proportion switched and median time till switch with corresponding IQR. All analyses will be performed to describe both the proportion of patients switches as well as the time till switch.

9a. Proportion of antibiotic switches ITT Crude

- Mixed effects logistic regression model, outcome: antibiotic switch (binary)
- Random intercept and random effect per hospital
- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen based on model fit as determined by AIC
- Determinant: intervention period versus control period
- Outcomes will be reported as Odds ratio's with corresponding 95% confidence intervals

9b. Proportion of antibiotic switches ITT Adjusted

- As (9a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment

10a. Time till antibiotic switch ITT Crude

- Mixed effects cox regression model, outcome: time till antibiotic switch (continuous)
    - Competing endpoint: mortality
- Random intercept and random effect per hospital

- Time as fixed linear effect
- Cluster autocorrelation will be checked by visually inspecting residuals
    - If cluster autocorrelation is present, an appropriate method for correction will be chosen
- Determinant: intervention period versus control period
- Outcomes will be reported as Rate ratio's with corresponding 95% confidence intervals

10b. Time till antibiotic switch ITT Adjusted

- As (10a), with:
- Adjustment for confounding co-variates: age, gender, PSI-score, smoking status, COPD, cardiac disease, diabetes mellitus, antibiotic pre-treatment