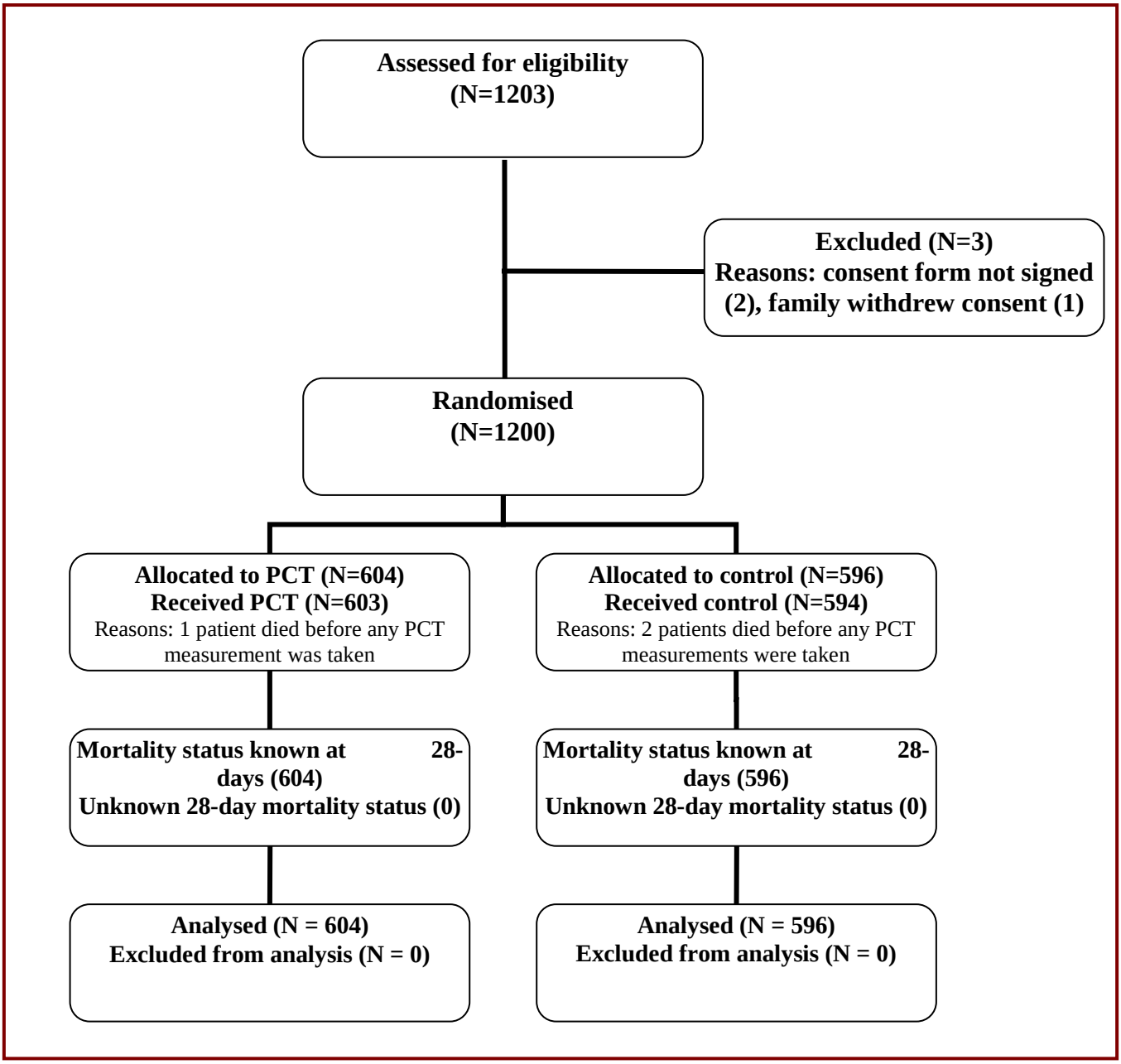
PASS-II **25th Aug 2010**

Antibiotics and Renal Organ Failure – secondary endpoints from the Procalcitonin And Survival Study - analysis plan

1. Consort Flow Diagram (done in PASS-1)



Trial profile.

2. Baseline characteristics

Table 1: Baseline characteristics

	Standard-of-care-only n=596)	Procalcitonin-guided n=604)	Overall n=1200)
Age (Yr.) Median (IQR)	67 (58–75)	67 (58–76)	67 (58–76)
Male sex – no. (%)	333 (55·9%)	330 (54·6%)	663 (55·3%)
Body Mass Index – Median kg/m2 (IQR)	24·7 (22·0–27·8)	25·0 (22·5–28·7)	24·8 (22·2–27·9)
APACHE II Score - Median (IQR)	18 (13–24)	18 (13–25)	18 (13–24)
Surgical patient – no. (%)	260 (43·6)	227 (37·6)	487 (40·6)
Chronic co-morbidity* - no. (%)			
No chronic co-morbidities	102 (17·1)	123 (20·4)	225 (18·8)
1 chronic co-morbidities	279 (46·8)	257 (42·6)	536 (44·7)
2 chronic co-morbidities	173 (29·0)	171 (28·3)	344 (28·7)
≥3 chronic co-morbidities	42 (7·1)	53 (8·8)	95 (7·9)
Acute illness/reason for admittance to ICU – no. (%)			
Central nervous system incl. Unconsciousness	78 (13·1)	101 (16·7)	179 (14·9)
Respiratory failure	422 (70·8)	410 (67·9)	832 (69·3)
Circulatory failure	263 (44·1)	257 (42·6)	520 (43·3)
Gastro-intestinal disease	128 (21·5)	96 (15·9)	224 (18·7)
Renal disease	81 (13·6)	103 (17·1)	184 (15·3)
Post-operative complications	123 (20·6)	106 (17·6)	229 (19·1)
Trauma	113 (19·0)	106 (17·6)	219 (18·3)
Other	68 (11·4)	57 (9·4)	125 (10·4)
Indicators of severity			
Temperature, ^{0}C (median (IQR), n=1136)	37·3 (36·3–38·1)	37·4 (36·4–38·3)	37·3 (36·3–38·2)
Mean arterial pressure, mmHg (median (IQR) n=1195)	71 (60–84)	72 (63–85)	71 (62–84)
Heart frequency (median (IQR) n=1197)	100 (82–116)	100 (84–117)	100 (83–117)
Need for vasopressor/inotropic drug† (%, n=1200)	315 (52·9)	326 (53·4)	641 (53·4)
PaO2 /PaCO2 ratio (median (IQR), n=1178)	1·85 (1·27–2·62)	1·82 (1·29–2·53)	1·83 (1·28–2·59)
pH (median (IQR) n=1185)	7·29 (7·21–7·39)	7·29 (7·20–7·38)	7·29 (7·20–7·38)
Mechanical ventilation used (%, n=1200)	401 (67·3%)	401 (66·4%)	802 (66·8%)
Creatinine µmol/lL (median (IQR) n=1167)	119 (78–197)	119 (75–208)	119 (76–202)
Dialysis required (%, n=1200)	88 (14·8%)	86 (14·2%)	174 (14·5)
Bilirubin, µmol/L (median (IQR) n=1109)	10 (6–17)	10 (5–18)	10 (5–17)
Infection, clinical assessment ‡ – no. (%)			
No infection	118 (19·8)	86 (14·2)	204 (17·0)
Localized infection or Sepsis	266 (44·6)	271 (44·9)	537 (44·8)
Severe sepsis/ septic Shock	212 (35·6)	247 (40·9)	459 (38·3)
Site of infection § – no. (%)			
CNS	12 (2·0)	35 (5·8)	47 (3·9)
Respiratory	292 (50·0)	324 (53·6)	616 (51·3)
Gastrointestinal	149 (25·0)	145 (24·0)	294 (24·5)
Urinary	28 (4·7)	42 (7·0)	70 (5·8)
Other	52 (8·7)	41 (6·8)	93 (7·8)
Biomarkers			
Alert-PCT || – no. (%)	279 (47·0)	312 (51·7)	591 (49·4)
Leukocytes, x10^{9} – median (IQR)	13·0 (8·8–18·1)	12·4 (8·0–18·1)	12·8 (8·4–18·1)
C-reactive protein, mg/L – median (IQR)	152 (54–266)	161 (56–271)	157 (56–271)

Interquartile range (IQR). Acute Physiology and Chronic Health Evaluation II score (APACHE II) ranges from 0 to 71. *Chronic co-morbidity: Earlier diagnosed via hospital admission: heart failure, lung disease, cancer, diabetes, alcohol abuse, chronic infection, neurological disease, renal diseases, liver disease, gastro-intestinal disease, autoimmune disease, cancer and psychiatric disorders. Acute illness: persons can have several. 'Other' includes liver disease, haemorrhage, haematological disease and poisoning. †Vasopressors/inotropic drugs are considered to be epinephrine, nor-epinephrine, dopamine and dobutamine. ‡ Infections were rated according to the ACCP/SCCM definitions; investigators were trained in using them. § Site of infection: patients can have more than one. ||Alert-PCT: Procalcitonin-level not decreasing by at least 10% from the previous day and above 1·0 ng/ml. If only one measurement is available: Absolute procalcitonin-level above 1·0 ng/ml.

Table 1. Baseline characteristics of the study participants.

Table 2: Follow up characteristics

Follow up measurement	Control group (N=596)	PCT-guided group (N=604)	Overall (n=1200)
Patients followed and alive for 28 days (N., %)			
Patients followed for 28 days (incl. those who died in the first 28 days) (N., %)			
Status at 28 days (n =): Alive Dead			
Days spent in ICU Median (IQR) (as in PASS-I)			
Days spent in Danish hospital within 28 days Median (IQR)			
Patients with a complete 28 day follow up for respiratory failure (mech. Vent., PaO2 and FiO2)			
Days followed within 28 days for respiratory failure (mech. Vent, PaO2 and FiO2) of total days in trial ((denom. = 604 x 28) this can be drawn from the admission list in combination w. database)			
Patients with 28 day follow up for renal failure (dialysis – same as prev.)			
Days followed within 28 days for renal failure (dialysis) of total days in trial (denominator = 604 x 28 and 596 x 28 days) (same as prev.)			
Patients with 28 day follow up for renal failure (eGFR)			
Days followed within 28 days for renal failure (eGFR) of total days in trial (denominator = 604 x 28 and 596 x 28 days)			
Patients with 28 day follow up for Platelets			
Patients with 28 day follow up for Bilirubin			
Patients with 28 day follow up for antibiotic consumption			

n*s refers to the total number of patients who had follow up for 28 days.
28-day follow up is: Follow up until death within 28 days OR until day 28. For respiratory failure follow up is done for all ICU admissions. For renal failure, follow up is done for all dialysis treatment (ICU+other dialysis competent hospital units) and for all creatinine and carbamide measurements performed within 28 days (ICU + non-ICU admissions). For platelets and bilirubin, follow up is done for all measurements performed within 28 days (ICU + non-ICU admissions)

STRATIFICATION (*S) / test for interaction: (regarding the below analyses in Section 2 + 3)

1. **Age (limit initially 65 y, if significant interaction, more age groups**
2. **APACHE II score (limit initially 20, if significant interaction, more APACHE II groups,**
3. **Site 1-9.**
4. **Severe Sepsis/septic Shock vs. Milder or No infection at Baseline**
5. **Calendar date of inclusion into PASS. Recruited: 9th Jan 2006 – 31st December 2007 (~430 patients) vs. 1st of Jan 2008 – 2nd of June 2009 (~770 patients).**

6. **Surgical patient / medical patient [Surgical = All patients with mark in Baseline "B6", or "B12" or marked "Yes" in "L"]**

7. **Gender**

SECTION 2. Exposure – Antibiotic usage

Follow up: All patients were followed up regarding antibiotic consumption: 1) In the ICU in the primary PASS-CRF, 2) All ICU-surviving patients, not staying in the ICU for 28 days, were followed up for antibiotic consumption in the non-ICU, they were discharged to after ICU.

General: The aims of these analyses are to investigate the impact of performing PCT-guided empiric antibiotic interventions according to a progressive algorithm on the consumption of antibiotics. This is to be illustrated by analyses exploring 1) spectrum, 2) quantity and 3) duration of therapy in the two arms.

The aim is:

a) To investigate the difference in exposure in general to antibiotics in the two arms of the PASS trial and more specifically to broad-spectrum antibiotics.

This is done in the following analyses (PCT vs. Control):

1) The total number of days within the 28 day follow-up period with any antibiotic treatment (or proportion of follow-up time): [Not done Yet]
2) The total consumption of any antibiotic in weight (grams within 28 days) [Not done Yet]
3) The total consumption per ICU day of any antimicrobial [DONE]
4) The total consumption of betalactam drugs active against most Extended Spectrum Beta-lactamases and wild-type Pseudomonas aeruginosa (a. Meropenem and other pseudomonas active carbapenems, OR b. Piperacillin/tazobactam OR c. 4.generation Cephalosporins). [or proptortion of days in these treatments] [Not done Yet]
5) The total no. of days within the 28-day follow up period with treatment with any flour-quinolone (ciprofloxacin, moxifloxacin and others) [or proptortion of days in these treatments] [Not done Yet]
6) The total no. of days within the 28-day follow up period with treatment with any glycopeptide (Vancomycin, Teicoplanin) [or proptortion of days in these treatments] [Not done Yet]
7) The total no. of days within the 28-day follow up period with treatment with fluconazole [or proportion of days in these treatments] [Not done Yet]

Consumption of antimicrobials in the intensive care unit				
Length of antimicrobial treatment in ICU, days (median, IQR)	4 (3– 10)	6 (3– 11)	-	0·001
Quantity of antimicrobials administered per ICU day (g) (median, IQR)	6·7g (4·5g– 12·5g)	8·6g (5·3g– 13·7g)	-	<0·001
Number (%) ICU days spent with at least three antimicrobials	2721 (57·7%)	3570 (65·5%)	-7·9% (-9·7%– -6·0%)	0·002

*Counted from the time of sampling. Only samples later to become positive. Cultures with coagulase negative staphylococci, corynebacteria and propionebacteria are not included. † Including localised infection, mild sepsis, severe sepsis and septic shock. p-values for the number of days spent with each factor were generated by testing the proportion of intensive care days spent with each factor using non-parametric tests. ICU: Intensive care unit

Table 3. Antibiotic consumption

Admission time within 28 days

1. Number of days admitted to hospital within 28 days after recruitment. Median + IQR. (PCT vs. Control)

Subgroup Analysis: Total use of Antimicrobial chemotherapy

1. Total antibiotic prescription days (all AMCs received, where all AMCs are weighted equally and summed per day, e.g.:→ possible to have e.g. 30 prescription days in 10 days ICU)

Table 3: Number of AMCs received per day (over all days)

	PCT-arm	Control-arm	P-value
AMC total (N,. %)			
Recruited 09/01/06 – 31/12/07 Recruited 01/01/08 – 02/06/09			
Age <65 years Age ≥65 years			
APACHE II <20 APACHE II ≥20			
Bispebjerg Gentofte Glostrup Herlev Hillerød Hvidovre Roskilde Skejby Århus			
Severe Sepsis or septic shock at BL Milder or no infection at BL			
Surgical patient Non-surgical patient			
Gender			

MICROBIOLOGY

Follow up: All patients were followed up via the electronic registers at the microbiologic depts., who service the PASS-ICU´s regarding all microbiologic samples performed from baseline and until 28 days after. Data have been merged in the PASS-database.

Table 4: Number of culture samples performed within 28-days from randomisation [Not done Yet – JU handles this]

Intervention		**PCT arm N =**	**Control Arm N =**	**P-value**
Microbiology:	**N., (%)**			
Blood Cultures	N. Yes, (%)			
Urine Cultures	N. Yes, (%)			
Airway Cultures	N. Yes, (%)			
Samples from other foci	N. Yes, (%)			

SECTION 3a: Estimating the degree of Organ Failure (OF)

Follow up: All patients were followed up regarding respiratory failure (mech. Vent + physiologic parameters) and renal failure at 1) the PASS-ICU where the patient was recruited in the primary PASS-crf, 2) regarding mech. Ventilation and physiologic parameters and renal failure at any other PASS-ICU within the 28 day period (when patients were discharged to such an ICU, 3) in the case that a patient was discharged within the 28 day period to a non-PASS ICU (seldom), follow up was made for mech. Vent. and physiologic parameters and renal failure in hospitals "Rigshospitalet" and "Bispebjerg", since only very few ICU days were spent at any other ICU within the 28 day period (48 days of approx 9900 days = approx 0.5%).

The purpose of these analyses is to explore in detail, the quantity of the occurrence of secondary endpoints in the PASS-trial, especially respiratory organ failure and renal organ failure.

Genuine hypothesis: High usage of broad spectrum antibiotics as used in the PASS trial, results in substantially reduced organ function (respiratory, renal and liver) and compromised coagulation and a likewise substantially increased time with manifest organ failure as defined clinically (need for organ support) AND biochemically/fysiologically (measured objective parameters).

NB: Analyzes are summarized in the table 5 below

time)

A. Renal Failure:

a. Median/ Mean eGFR for day1 – day10
b. Median/ Mean eGFR for day11 – day28
c. Median/Mean eGFR for day1 – day28 (a+b) [eGFR on days in columns in a figure and AUC for the columns]
d. Median/Mean Carbamide for day1- day10
e. Median/ Mean Carbamide for day11 – day28
f. Median/Mean Carbamide for day1 – day28 (a+b) [Carbamide level on days in columns in a figure and AUC for the columns]
g. Median/Mean Platelet count for day 1-28 [[platelet on days in columns in a figure and AUC for the columns]
h. Median/Mean Bilirubin [Bilirubin on days in columns in a figure and AUC for the columns]
i. No. of days within 28 days with eGFR < 60 ml/min/1.73 m2
j. No. of days within day1 – day10 with eGFR < 60 ml/min/1.73 m2
k. No. of days within day1 – day10 with dialysis
l. No. of days within day11 – day28 with dialysis
m. No. of days within day1 – day28 with dialysis

C + F+ G + H are all part of one figure with 4 panels.

Explanations: A: Dialysis:

Patients are categorized on days with ND or NA as dialysis=0, since this means patient has been discharged to home. All admissions within 28 days have been drawn from the central hospital register (Green System) and all admissions at dialysis capable departments have been followed up with dialysis.

B: eGFR:

In the ICU, patients are categorized with a new eGFR every day (done in PASS).

Patients are categorized on the basis of their status of eGFR on the last day of ICU. This status is kept until a creatinine measurement is done (on which day the status is changed to a new eGFR). This status is then kept until the next time creatinine is measured – and so forth. In this way every day from 1 – 28 is given an eGFR status.

In summary, the same principle is used: From day 1, the first time a creatinine is measured, a eGFR is calculated. Next time the patient has a creatinine measurement, the patient is re-categorized with a new eGFR. That eGFR is kept until the next creatinine measurement etc.

Table 5. Prevalence and duration of organ failure and other severe disturbances (PCT vs. Control)

	PCT arm (n =)	**Control Arm (n =)**	**P-value**
Kidney Failure mL/min/1.73 m^2 (N. days, % of total days): Normal: GFR > 90 Mildly impaired: 60–89 Moderately/severely impaired: GFR <60			
Kidney Failure Median/ Mean eGFR for day1 – day10			
Kidney Failure Median/ Mean eGFR for day11 – day28			
Kidney Failure Median/Mean eGFR for day1 – day28 (a+b)			
Kidney Failure Median/Mean Carbamide for day1- day10			
Kidney Failure Median/ Mean Carbamide for day11 – day28			
Kidney Failure No. of days within 28 days with eGFR < 60 ml/min/1.73 m2			
Kidney Failure No. of days within day1 – day10 with eGFR < 60 ml/min/1.73 m2			
Kidney Failure No. of days within day1 – day10 with dialysis			
Kidney Failure No. of days within day11 – day28 with dialysis			
Kidney Failure No. of days within day1 – day28 with dialysis			

Table with summarized analyses.

SECTION 3b: Attempting to explain the reason for organ failure (if OF is confirmed in section 3a)

Antimicrobial toxic explanation

Genuine hypotheses:

1) High Exposure (at least 5 or at least 10 days) to a certain combination of antibiotics (Pip/Tazo+Cipro OR Meropenem + Cipro OR Pip/Tazo + Vanco OR Meropenem + Vanco) causes OF

For 2-6: Estimate accumulated risk for day 1, 2, 3 etc. separately in both PCT group and control group.

2) Treatment for more than 4 days with Pip/Tazo causes OF (also 10 days)
3) Treatment for more than 4 days with Ciprofloxacin causes OF (also 10 days)
4) Treatment for more than 4 days with Meropenem causes OF (also 10 days)
5) Treatment for more than 4 days with Vancomycin causes OF (also 10 days)
6) Treatment for more than 4 days with Cefuroxim causes OF (also 10 days)

For the below analyses two composite endpoints are used for the Pulmonary/renal OF:

1) **Organ failure endpoint A**: Clinical Organ Failure judgment: Endpoint=1 for any day with dialysis. If both are present, Endpoint=2. Results are presented as “Clinical Organ Failure Days”
2) **Organ failure endpoint B:** Objective Organ failure measures: Endpoint =1 for any day with eGFR <30, repeated with <60 ml/min/1,73 m2. “Objective Organ Failure Days”

Analyses:

A. Objective Organ failure endpoint:

As above, 1) – 6).

1) Analyze the median “Objective Organ Failure Days” to occur from “P-T treatment day 5” until 10 days later (counting endpoints for next 10 days). Censor at death.
2) Analyze the median “Objective Organ Failure Days” to occur from “Meropenem treatment day 5” until 10 days later (counting endpoints for next 10 days). Censor at death

B. Multiple Effects models:

Regarding renal dysfunction: Analyze renal recovery in eGFR progression per day on different drugs day 1-10 (Meropenem / Piperacillin-tazobactam / Ciprofloxacin / Cefuroxim), control for other known predictors of renal failure. Additionally after discontinuation of these drugs.

Sensitivity analyzes:

Cox or Logistic Regression ?

Endpoint: Binary endpoint. To be defined according to the median number of organ failure days within 10 days after exposure for 5 days.

Endpoint 1a: [>median number of “clinical organ failure days”]

Endpoint 1b: [>median number of “clinical organ failure days”+2 days]

Endpoint 2a: [>median number of “objective organ failure days”]

Endpoint 2b: [>median number of “objective organ failure days”+2 days]

Risk variables to be entered:

a. Treatment for >=4 days with Pip/tazo
b. Treatment for >=4 days with Meropenem
c. Treatment for >=4 days with Ciprofloxacin
d. Treatment for >=4 days with Vancomycin
e. Treatment for >=4 days with Pip/tazo + Ciprofloxacin (all 4 days)
f. Treatment for >=4 days with Meropenem + Ciprofloxacin (all 4 days)
g. Treatment for >=4 days with Pip/tazo + Vancomycin (all 4 days)
h. Treatment for >=4 days with Meropenem + Ciprofloxacin (all 4 days)
i. Treatment for >=4 days with Meropenem + Vancomycin (all 4 days)
j. APACHE II >=20
k. Age >=65
l. Surgical patient
m. Severe sepsis/septic shock

NB: Treatment count start days 1 – 13 (so 5 days complete on day 5 – 18).

Patients with pauses in the administration of >=1 day → exclude

Only count the first administration

Endpoints:

“Clinical Organ Failure Days” and “Objective Organ Failure Days” both as defined above

→Transformed to Binary endpoint:

Endpoint 1a: [>median number of “clinical organ failure days”]

Endpoint 2a: [>median number of “objective organ failure days”]

(as above in the sensitivity analysis)

PASS-II, organ failure – authors,
Forfattere

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KMA Hvh/Diacenter: BEL

Glostrup: Mulige: Asger, Anne, Ditte

Hvh: Mulige: Peder C, Jesper, Morten

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Gentofte: Mulige: Thomas, Katrin

Hillerød: Mulige: Morten, Lars, Kristian A?

Roskilde: Mulige : Niels-Erik

Århus: Mulige: Kim + Mads

Skejby: Mulige: Paul