



# Rivastigmine bij delirium

## Lessen van een voortijdig beëindigde trial

Dr. A.J.C. Slooter

Topics in Intensive Care, 8 december, 2011

# Funding and Conflict of Interest

ZonMw Grant number 80-82305-98-08109



Netherlands Brain Foundation Grant number 2008(1).30



Novartis

*Supplied the study medication*

*No role in initiation, design, conduct, interpretation or presentation*



University Medical Center Utrecht



1. Design and results of the trial

2. Lessons for the future

# Delirium

# Frequency and Impact

Frequent disorder in the ICU

*Up to 80% of patients*

Associated with poor prognosis

*Longer ICU and hospital stay, increased risk of cognitive decline, higher mortality*

Associated with higher costs

# Treatment

Treat underlying disorder

Quiet environment, frequent orientation

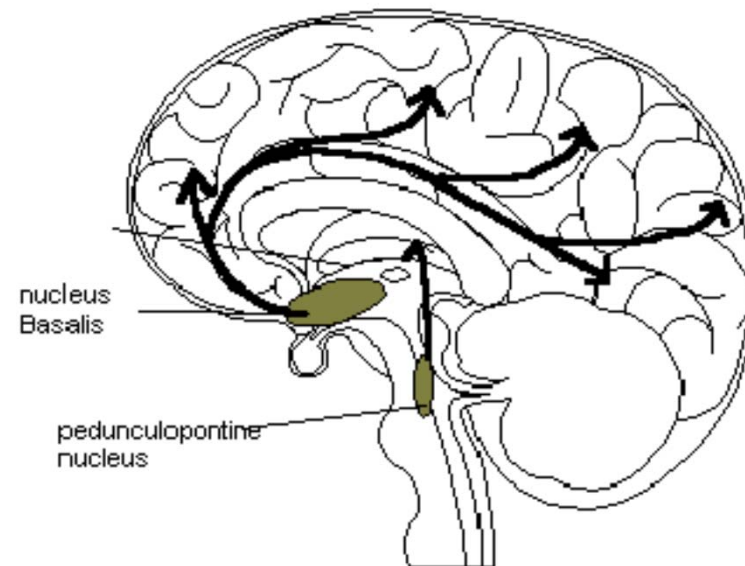
Antipsychotic: haloperidol

Benzodiazepine

Cholinesterase inhibitor?

# Impaired Cholinergic Transmission

## major cholinergic projections



**Nucleus basalis projects to the neocortex**  
**PPN projects to the thalamus**

# Impaired Cholinergic Transmission

Drugs with anticholinergic effects can cause delirium

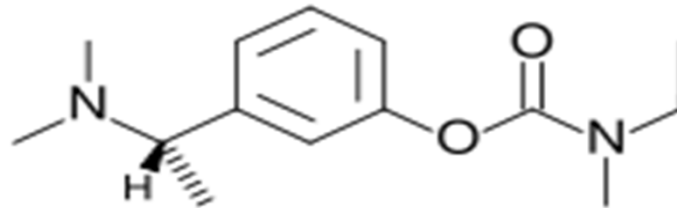
Serum anticholinergic activity is increased in delirium

Persistent delirium may be treated with cholinesterase inhibitors  
such as rivastigmine

# Rivastigmine

Inhibitor of acetyl- and butyrylcholinesterase

Approved for the symptomatic treatment of Alzheimer's Disease,  
Parkinsons Disease Dementia and Lewy Body Dementia



# Hypothesis

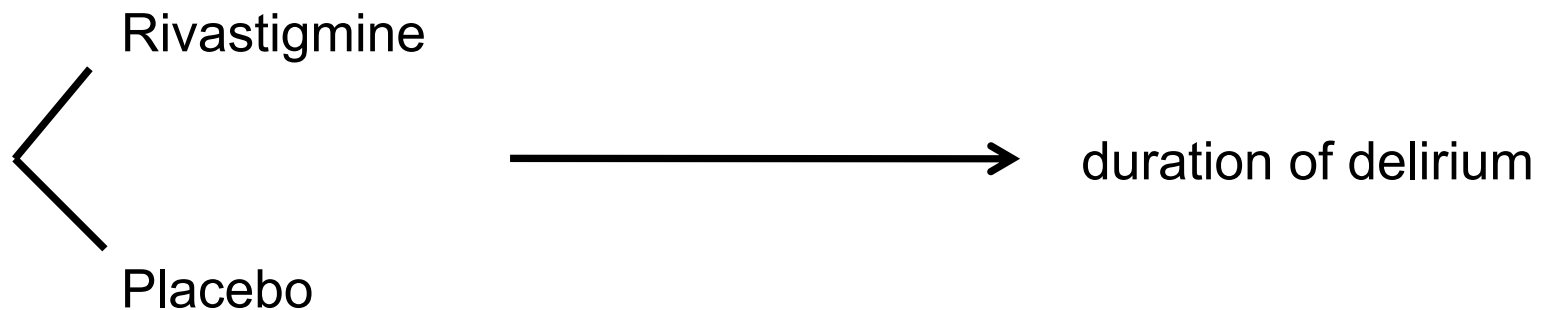
Rivastigmine added to usual care reduces the duration of delirium in critically ill patients



# Methods

# Trial Design

Multicentre, double-blind, randomized, placebo-controlled, add-on



Added to usual care

ClinicalTrials.gov NCT00704301

# Study Group

**MCL Leeuwarden**

M.A. Kuiper

**MCA Alkmaar**

M.L.H. Honing

**Gelre Hospital Apeldoorn**

P.E. Spronk

**Diakonessenhuis Utrecht**

A. Karakus

**UMC Utrecht**

M.M.J. van Eijk

A.J.C. Slooter

**EMC Rotterdam**

M. van der Jagt



# Study Group

M.M.J. van Eijk, coordinating investigator

Prof. K.C.B. Roes, biostatistician

Prof. W.A. van Gool, neurologist

Prof. R.C. van der Mast, psychiatrist

Prof. J. Kesecioglu, director

A.J.C. Slooter, principal investigator

# Study Population

## **Inclusion criteria**

Positive CAM-ICU

18 years or older

Expected ICU stay > 48 hours

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## **Exclusion criteria**

Pregnant or lactating

Unable to receive enteric medication

Renal replacement therapy

Liver failure with hepatic encephalopathy

Known allergy to rivastigmine

Second or third degree AV block or bradycardia

Doubts about the delirium diagnosis

No informed consent

# Usual Care

Nursing protocol with frequent orientation

Haloperidol:

≥ 70 yrs: 3x1 mg iv

< 70 yrs: 3x2,5 mg iv

Benzodiazepine:

Lorazepam 1 mg *ante nocte*

# Study Medication

Day 1-3: 2x1.5 mg

Day 4-6: 2x3 mg

Day 7-9: 2x4.5 mg

Day 10 – end of study: 2x6 mg

Solutions were similar with regard to colour, smell, taste and viscosity

# Study Medication

Continued until:

- End of delirium (CAM-ICU 48 hours negative)
- Discharge
- Death

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In case of side effects:

- Reduced until the side effect resolved
- Stopped if the side effect persisted > 3 days

# Escape Medication

Haloperidol

≥ 70 yrs: 2,5 mg iv every 30 min.

< 70 yrs: 5 mg iv every 30 min.

Sedation

Propofol tapered every 12 hours

Midazolam tapered every 12 hours

# Sample Size Estimation

Assumptions:

Duration of delirium: 3.4 (mean; SD 1.9 days)

80% power, alpha = 0.05, 1:1 randomization

To detect a reduction of 0.5 day:



Sample size: 2x220 patients

# Data Analysis

Intention-to-treat analysis

Primary outcome: duration of delirium

*Mann-Whitney test and Cox's regression analysis*

# Data Analysis

Secondary outcomes:

- mortality

*Kaplan-Meijer, log rank statistics, Cox's regression*

- severity of delirium
- psychoactive medication use
- length of ICU and hospital stay

*Mann-Whitney tests*



# Results



# Interruption

Dr. R.J. van Marum, chairman of the DSMB:

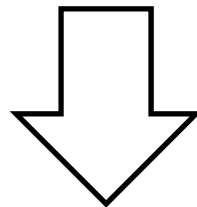
*“.... there is a 3-times higher mortality rate in the rivastigmine group without any relevant baseline imbalances. Furthermore, there is no noticeable beneficial effect of the rivastigmine. We advise to terminate the study.”*



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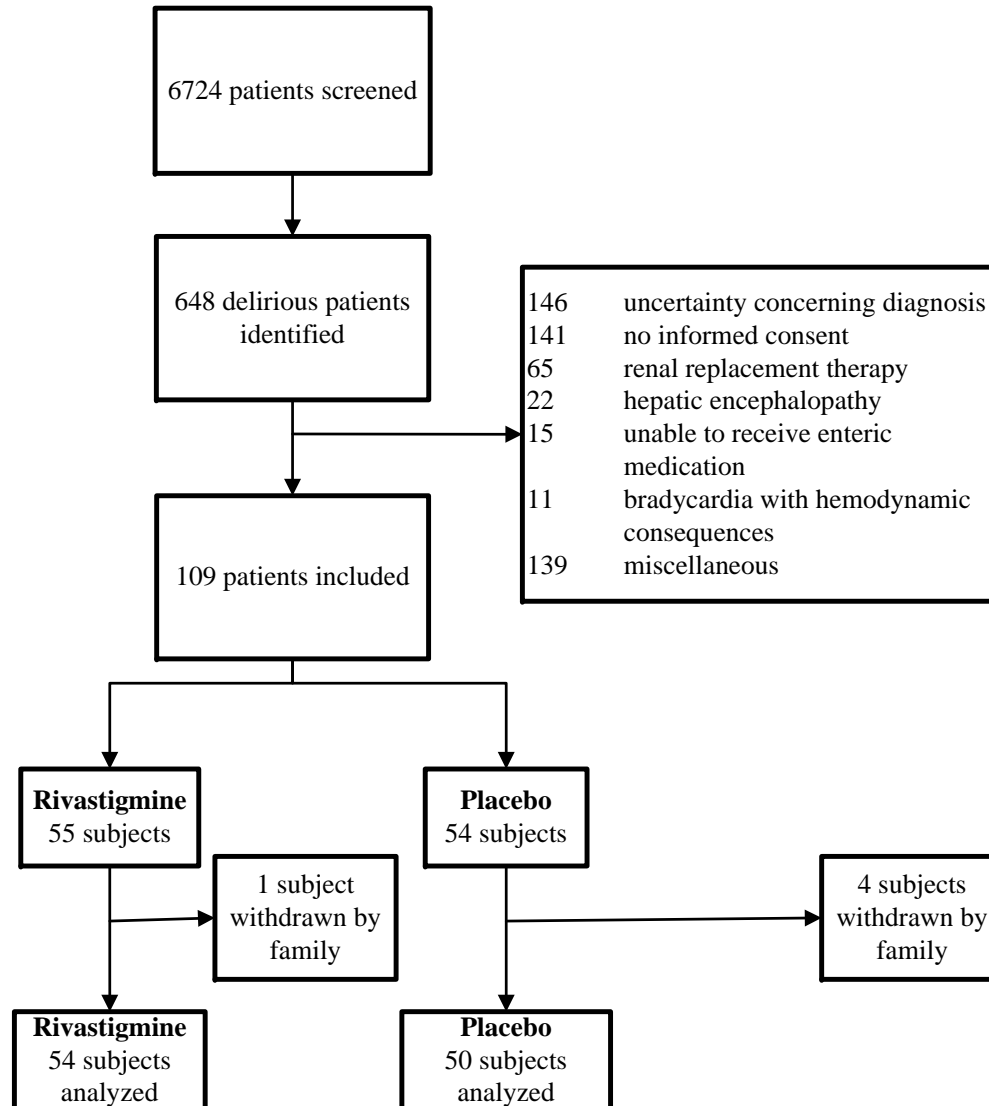
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Halted after the 4<sup>th</sup> interim analysis and inclusion of 104 patients

# Inclusion



# Baseline Characteristics

	<b>Rivastigmine (n=54)</b>	<b>Placebo (n=50)</b>
<b>Age, mean (SD)</b>	68.0 (11.4)	70.0 (12.2)
<b>Male gender, n (%)</b>	38 (70%)	29 (58%)
<b>APACHE II score, mean (SD)</b>	20.3 (8.9)	19.6 (7.9)
<b>Admitting discipline, n (%)</b>		
- Internal medicine	17 (31%)	15 (30%)
- General surgery	21 (39%)	16 (32%)
- Cardiology/cardiothoracic surgery	13 (24%)	18 (36%)
- Neurology/neurosurgery	3 (6%)	1 (2%)
<b>Emergency admission, n (%)</b>	46 (87%)	32 (64%)
<b>Estimated hours of delirium before inclusion, median; IQR</b>	12.0 (5.8 – 36.0)	12.0 (6.5 – 22.5)

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	Rivastigmine	Placebo	p-value
<i>All patients</i>	5.0 (2.7 - 14.2) n=54	3.0 (1.0 - 9.3) n=50	0.06

Mann-Whitney-U test

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<i>All patients</i>	5.0 (2.7 - 14.2) n=54	3.0 (1.0 - 9.3) n=50	0.06
<i>End delirium</i>	4.0 (2.0 - 16.0) n=35	2.5 (1.0 - 5.8) n=34	0.06

Mann-Whitney-U test

# Primary Outcome

## Delirium duration in days, median; IQR

	Rivastigmine	Placebo	p-value
<i>All patients</i>	5.0 (2.7 - 14.2) n=54	3.0 (1.0 - 9.3) n=50	0.06
<i>Discharge</i>	6.0 (3.5 - 11.5) n=7	6.0 (3.0 - 21.5) n=12	0.95

Mann-Whitney-U test

# Primary Outcome

## Delirium duration in days, median; IQR

	Rivastigmine	Placebo	p-value
<i>All patients</i>	5.0 (2.7 - 14.2) n=54	3.0 (1.0 - 9.3) n=50	0.06
<i>Death</i>	9.5 (4.8 - 11.8) n=12	8.0 (1.0 - 9.0) n=4	0.29

Mann-Whitney-U test

## Secondary Outcomes: Mortality

### During study treatment

Rivastigmine	Placebo	p-value
n=12 (22%)	n=4 (8%)	0.07

Chi-Square test

## Secondary Outcomes: Mortality

### During study treatment

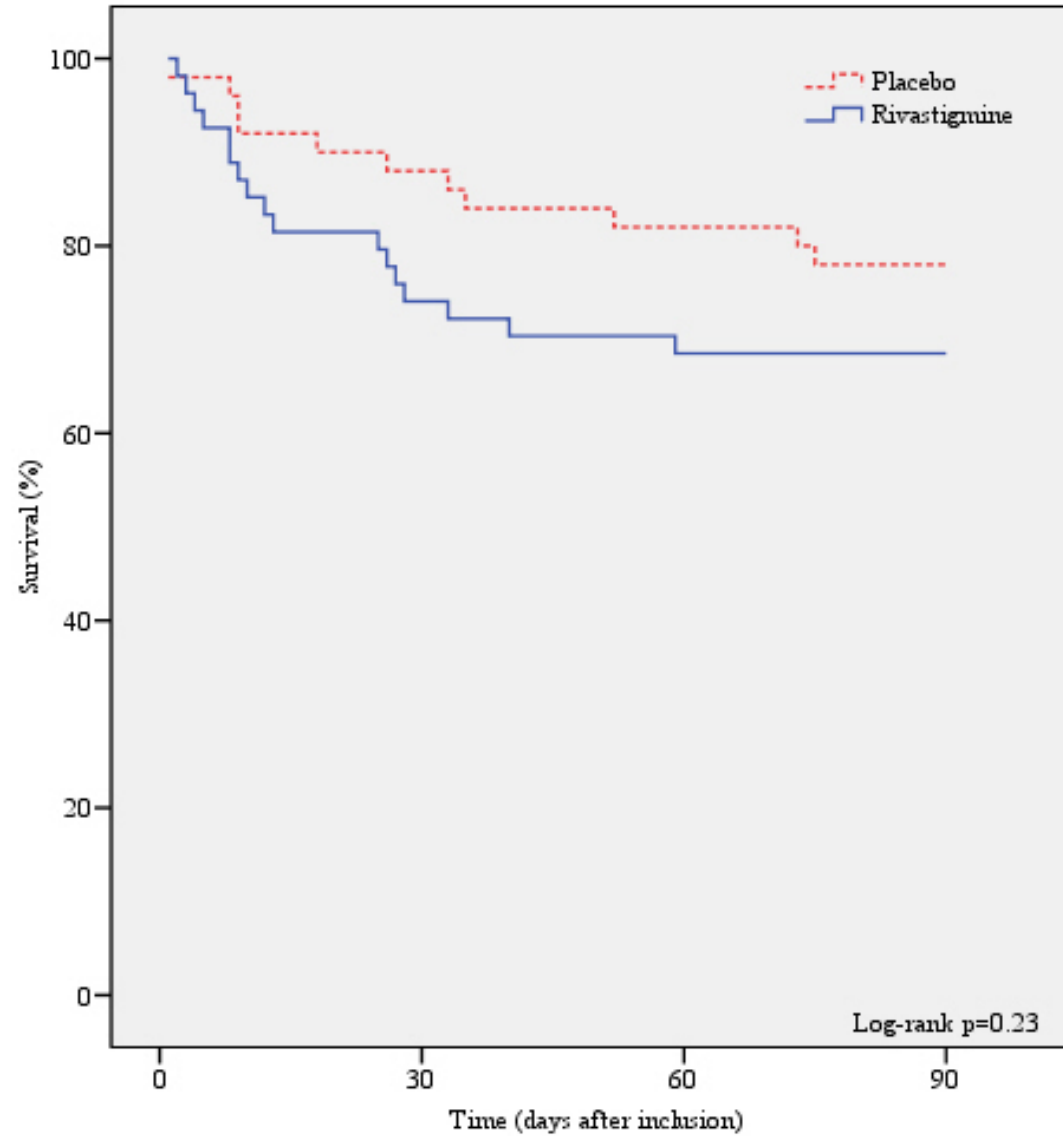
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n=12 (22%)	n=4 (8%)	0.07

### After 90 follow-up days

n=18 (33%)	n=11 (22%)	0.14
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Chi-Square test

# Secondary Outcomes: Mortality



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## Causes of death:

	Sex	Age (years)	APACHE II score	SOFA score*	Duration of study (days)	Dose of study drug (mL)*	Intervention	Short case history	Autopsy
Patient 1	Female	66	26	9	10	3	Rivastigmine	Type A aortic dissection followed by asystole due to recurrent heart tamponade for which several thoracotomies were done; long stay in intensive care unit; died of heart failure due to several myocardial infarctions	Yes
Patient 2	Male	74	22	15	34	0.75	Rivastigmine	Acute pancreatitis, several events of septic shock, and abdominal surgery; died of multiorgan failure, including disseminated intravascular coagulation and intestinal ischaemia	Yes
Patient 3	Male	70	30	13	5	0.75	Rivastigmine	Chronic renal failure and abdominal aortic aneurysm for which endograft placement was done, but became infected with <i>Staphylococcus aureus</i> , resulting in septic shock; persistent endograft leakage resulting in death	Yes
Patient 4	Female	69	16	12	9	0	Placebo	Abdominal aortic endograft with rupture of anastomotic aneurysm; postoperative septic shock due to intestinal ischaemia; died of rupture of recurrent aneurysm	Yes
Patient 5	Male	77	19	6	10	2.25	Rivastigmine	Amputation because of severe peripheral arterial disease; respiratory failure and heart failure; died of pneumonia	No
Patient 6	Male	78	26	5	5	1.5	Rivastigmine	Colorectal carcinoma with peritoneal carcinomatosis, ileus, and abdominal sepsis; died of septic shock following bowel perforation during surgery	No
Patient 7	Female	59	20	8	14	0.75	Rivastigmine	Subarachnoid haemorrhage followed by hydrocephalus (ventricular drain and secondary meningitis); died of respiratory failure due to acute respiratory distress syndrome	Yes
Patient 8	Male	82	19	7	18	3	Placebo	Coronary artery bypass graft and aortic valve replacement, anticoagulation, recurrent rectal bleeding, cardiac arrest followed by renal failure and decubitus ulcers; died of recurrent sepsis	No
Patient 9	Male	74	11	13	11	0	Rivastigmine	Aortic valve replacement complicated by persistent bleeding and recurrent thoracotomy; died of multiorgan failure	No
Patient 10	Male	88	26	11	1	0.75	Placebo	Gastric ulceration complicated by pneumonia; died of severe sepsis with acute kidney failure	No
Patient 11	Male	57	40	12	4	0.75	Rivastigmine	Multiple myeloma complicated by pneumonia, atrial fibrillation, and heart failure; no life sustaining treatment was started because of unfavourable prognosis; died of multiorgan failure	No
Patient 12	Male	55	23	16	8	1.5	Placebo	Chemotherapy for acute myeloid leukaemia; admitted to intensive care unit for pneumonia resistant to antibiotic treatment; died of multiorgan failure	No
Patient 13	Female	75	17	2	3	0.75	Rivastigmine	Pancreatoduodenectomy for pancreatic carcinoma; postoperative acute septic shock based on anastomosis dehiscence; died of septic shock	Yes
Patient 14	Female	83	12	13	9	2.25	Rivastigmine	Ovarian carcinoma for which surgical debulking was done; postoperative anastomotic leakage from bowel with sepsis for which several abdominal surgeries were done; died of recurrent septic events and multiorgan failure	No
Patient 15	Female	62	38	4	18	1.5	Rivastigmine	Ileus; several abdominal operations complicated by ischaemic colon and sepsis; long stay in intensive care unit with recurrent septic events; died of multiorgan failure	No
Patient 16	Female	80	6	6	8	1.5	Rivastigmine	Hemicolectomy for colon carcinoma; postoperative hypovolaemic shock; subsequent operation led to septic shock and multiorgan failure, resulting in death	No

APACHE=acute physiology and chronic health evaluation. SOFA=sequential organ failure assessment. \* At 24 h before death.

**Table 3: Case series of patients who died during treatment**

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# Multivariate Analyses

Findings on delirium duration and mortality  
did not change with Cox's regression  
analysis and adjustments for baseline differences  
in gender and emergency admissions

# Other Secondary Outcomes

## Other Secondary Outcomes

*Total dose study medication (mg)*

	Rivastigmine	Placebo	p-value
Median	21.8	12.8	0.12

## Other Secondary Outcomes

### *Mean Delirium Severity Index*

	Rivastigmine	Placebo	p-value
Median	2.3	2.0	0.004

## Other Secondary Outcomes

*Median use of psychotropic medication (mg)*

	Rivastigmine	Placebo	p-value
Haloperidol	3.2	3.1	0.30
Lorazepam	0.2	0.0	0.28

Mean mg per patient per day

## Other Secondary Outcomes

*Median length of stay (days)*

	Rivastigmine	Placebo	p-value
ICU	15	8	<0.0001
Hospital	29	25	0.06



# Discussion

# Summary

Rivastigmine:

- No decrease in duration of delirium
- More severe delirium
- Longer ICU stay
- Increased mortality (NS)

# Strengths

- First large RCT on a cholinesterase inhibitor as treatment for ICU delirium
- Multicentre design
- Strict and complete follow-up
- Every 3 months interim analyses

## Implications (1)

- Difference in mortality not statistically significant (22% versus 8%;  $p=0.07$ )
- Causes of death were heterogeneous
- No evidence for a detrimental effect of rivastigmine



*Difference in mortality may be due to chance*

## Implications (2)

*Most important:*

No evidence for any beneficial effects

The median duration of delirium was even 2 days longer in the rivastigmine group ( $p=0.06$ )



**Conclusion**

# Conclusion

Rivastigmine should not be administered  
to delirious ICU patients

# Acknowledgement

All patients and their legal representatives

Medical and nursing staff in all centres

Study Group: Maarten van Eijk, Kit Roes, Marina Honing, Michael Kuiper, Attila Karakus, Mathieu van der Jagt, Peter Spronk, Pim van Gool, Roos van der Mast, Jozef Kesecioglu

Data-managers: Frank Leus and Joost Schotsman

Pharmacists in all participating centres

Michel Bots, Erik Buskens and Ardine de Wit

DSMB members: Dr. R.J. van Marum (chair), Dr. I. van der Tweel, Prof. P. Eikelenboom, Prof. J.M.A. Sitsen, Prof. E. de Jonge, Prof. D Zandstra,

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- 4 - Budget should be sufficient
- 5 - Do not include all possible trial centers
- 6 - Consider the optimal frequency of interim analyses

Thank you for your attention

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