# Right Dose, Right Now: Randomized Controlled Clinical Trial

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To assess the influence of dosing guided by AutoK on achieving PK targets and clinical endpoints in intensive care patients with sepsis.

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Hepatobiliary neoplasms malignant and unspecified |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON53354

**Source**
ToetsingOnline

**Brief title**
Right Dose, Right Now: Randomized Controlled Clinical Trial

### Condition

- Hepatobiliary neoplasms malignant and unspecified

**Synonym**
blood poisoning, infection, infectious disease, Sepsis

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Vrije Universiteit Medisch Centrum
**Source(s) of monetary or material Support:** ZonMW

### Intervention

**Keyword:** Antibiotics, Personalized medicine, Pharmacometrics, Prediction

## Outcome measures

### Primary outcome

PK target attainment in the first 24-hours. Targets are 100%-fT>4MIC for the beta-lactam antibiotics, AUC/ MIC>400 for vancomycin and fAUC/MIC *125 for ciprofloxacin.

### Secondary outcome

Time to PK target level, PK target attainment during therapy, attainment of clinical cure, length of ICU and hospital stay, delta Sequential Organ Failure Assessment (SOFA) score at 96 hours, days free of ventilator / hemofiltration / other organ support, ICU / hospital / 28 day / 6-month mortality, quality of life at hospital discharge (EQ-5D-5L) and after 6 months, societal costs (iMTA MCQ and iMTA PCQ after 6 months), days free of delirium.

We will assess physician compliance and satisfaction with AutoK and investigate whether its use is associated with an increase in PK/PD knowledge amongst healthcare workers.

# Study description

### Background summary

Sepsis is a major and growing problem. In the Netherlands alone, around 15.000 patients are diagnosed with severe sepsis each year. Despite major scientific efforts, including many failed clinical trials mainly focusing on inflammatory mediators and the introduction of care bundles, the mortality rate for severe sepsis still remains unacceptably high at around 30%. This is alarming, especially since the incidence of sepsis continues to increase and now exceeds that of colon cancer, breast cancer and AIDS combined.

Antibiotics are essential for treating sepsis. Their early and appropriate use has repetitively been shown to reduce mortality rates. However, achieving adequate antibiotic exposure in critically ill patients is a major challenge due to markedly different pharmacokinetic (PK) profiles in the critically ill. Nevertheless, doctors still rely on standard antibiotic dosing schemes, that were developed based on data from healthy volunteers and non-critically ill patients. Depending on patient characteristics, clinical course and therapy, this strategy may result in underdosing and/or drug-related toxicity during the course of intensive care treatment.

Therefore, we developed AutoKinetics (AutoK) software. AutoK aims to make use of patient data that is available from the electronic patient records, for example about fluid balance and renal function. Using this data, AutoK is able to give fast and precise dosing advice, using published pharmacokinetic models of any drug. AutoK runs on the computer at the bedside. Thus, advice is readily available, even before treatment is started, and is continuously updated as disease and therapy evolve: true personalized dosing.

We hypothesize that AutoK can improve antibiotic dosing, morbidity and mortality for severe sepsis.

**Study objective**

To assess the influence of dosing guided by AutoK on achieving PK targets and clinical endpoints in intensive care patients with sepsis.

**Study design**

Multicenter, randomized controlled, two-arm, parallel-group, superiority trial

**Intervention**

Patients will be randomized to one of two groups.

Group 1 (Control group): standard intravenous antibiotic therapy based on current clinical guidelines and practice. Standard therapy will include TDM for vancomycin, but not for the beta-lactams and ciprofloxacin. The standard antibiotic dosing schemes are:

o OLVG:
* Vancomycin: continuous infusion 1000 mg/24h
* Ciprofloxacin: 2 x 400mg
* Cefotaxim: 4 x 1000mg
* Meropenem: 3 x 1000mg

o VUmc:

* Vancomycin: 1 x 1000 mg
* Ciprofloxacin: 3 x 400 mg
* Ceftriaxon: 1 x 2000 mg
* Meropenem: 3 x 1000 mg

Local standard protocols allow for higher dosing in case of suspicion of atypical pneumonia, central nervous system infection or endocarditis.

Group 2 (Experimental group): Personalized antibiotics dosing guided by AutoK, based on PK models combined with patient data from the electronic patient record.

**Study burden and risks**

Possible benefits to the subject include improved clinical outcome as a result of improved antibiotic dosing. Further, if feasible and successful, individualized antibiotic dosing could be a major step forward in the treatment of sepsis, which is a significant source of worldwide morbidity and mortality.

Estimated risks are small given AutoK*s safety profile, dose warnings and mandatory dose verification by the treating physician, as explained in the investigational medical device dossier. Burden is limited to extra blood sampling from an existing line (6-10 samples of 4 ml per antibiotic) and participation in follow-up questionnaires.

We therefore believe that the benefits outweigh the risks and burden.

# Contacts

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# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

- Age >18 years
- Suspected / confirmed infection
- Suspected / confirmed lactate concentration > 2 mM OR treatment / imminent treatment with vasopressors
- Treatment / imminent treatment with one or more of the following antibiotics: vancomycin, ceftriaxone, meropenem, ciprofloxacine, cefotaxime.

## Exclusion criteria

None

# Study design

## Design

| | |
|---|---|
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Single blinded (masking used) |
| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 19-02-2018 |
| Enrollment: | 420 |
| Type: | Actual |

### Medical products/devices used

| | |
|---|---|
| Generic name: | AutoKinetics |
| Registration: | No |
| Product type: | Medicine |
| Brand name: | Cefotaxim PCH |
| Generic name: | Cefotaxime |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Ceftriaxon Hikma |
| Generic name: | Ceftriaxone |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Ciprofoxacine Kabi |
| Generic name: | Ciprofloxacin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Meropenem Fresenius Kabi |
| Generic name: | Meropenem |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Vancomycin Xelia |
| Generic name: | Vancomycin |
| Registration: | Yes - NL intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 11-01-2018 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 25-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

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|---|---|
| Approved WMO Date: | 29-06-2018 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | 2017-002478-37 |
| CCMO | NL61682.029.17 |
| Other | NTR kandidaat nummer 27792 |

# Study results

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|---|---|
| Date completed: | 02-02-2022 |
| Actual enrolment: | 252 |

**Summary results**
Trial is onging in other countries