PROTOCOL
Hydrocortisone for Prevention of Septic Shock
‘HYPRESS’
Placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of low dose hydrocortisone to prevent the development of septic shock in patients with severe sepsis

Supported by the Federal Ministry of Education and Research (BMBF)
Project-Code: 01 KG 07 01

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**Protocol-Synopsis**

**Title of Trial**

Hydrocortisone for Prevention of Septic Shock

A *placebo-controlled, randomised, double-blind study to investigate the efficacy and safety of low dose hydrocortisone to prevent the development of septic shock in patients with severe sepsis*

**Acronym**

HYPRESS

**EudraCT number**

2007-004401-10

**www.ClinicalTrials.gov**

NCT00670254

**Indication**

Severe Sepsis
Patients must meet **ALL** inclusion criteria:

1. Informed consent from patient, legal representative, proxy, or preliminary by independent medical consultant.
2. In women with child bearing potential an effective contraception with a failure rate < 1 % (for definition see 4.1).
3. Clinical evidence of **INFECTION** (may be present ≥ 48 hours) – At least one of a-d is required.
   a. Pathogenic micro-organism in blood, sputum, urine, or normally sterile body fluid
   b. Identified focus of infection (e.g. ruptured bowel, purulent drainage or sputum)
   c. Presence of granulocytes in normally sterile body fluid
   d. Clinically suspected infection without positive culture of pathogenic microorganism (e.g. new infiltrate in chest X-ray, treated pneumonia, necrotizing fasciitis, purpura fulminans)
4. Evidence of **SIRS** (may be present ≥ 48 hours) – At least two of a-d are required.
   a. Fever (≥38 °C) or Hypothermia (≤ 36 °C)
   b. Tachycardia (≥ 90 bpm)
   c. Tachypnea (≥ 20 bpm) or hyperventilation (PaCO₂ ≤ 33 mmHg [≤ 4.3 kPa], or mechanical ventilation
   d. Leukocytosis (≥ 12.000 / μl) or leukopenia (≤ 4.000 / μl) or ≥ 10 % immature forms
5. Evidence of **ORGAN DYSFUNCTION** (may NOT be present ≥ 48 hours – At least one organ dysfunction of a-e is required
   a. **Encephalopathy**: Reduced vigilance, disorientation, agitation, delirium etc. in the absence of psychotropic drugs
   b. **Acute renal dysfunction**: Oliguria: ≤ 0.5 ml/kg/h ≥ 2 h despite adequate volume replacement and/or creatinine increase > 2 x above the normal upper range, and/or need for renal replacement therapy.
   c. **Coagulation dysfunction**: Platelets ≤ 100.000/μl or more than 30 % decrease from baseline within 24 hours. Thrombocytopenia may not be due to haemorrhage or immunologically induced.
   d. **Pulmonary dysfunction/hypoxemia**: PaO₂ ≤ 75 mmHg [≤ 10 kPa] at room air or PaO₂/FiO₂ ≤ 250 mmHg [≤ 33 kPa] with oxygen application. Hypoxemia may not be due to primary cardiac or pulmonary dysfunction (e.g. emphysema)
   e. **Microcirculatory dysfunction**: Lactate > 1.5 x above the normal upper range and/or base deficit ≥ 5 mmol/l and/or metabolic acidosis with pH < 7.3 and/or depressed capillary refill/mottling and/or significant body edema (capillary leakage syndrome)

Patients will be excluded for **ANY ONE** of the following reasons:

1. **Sepsis-induced HYPOTENSION** despite adequate volume replacement defined as a mean arterial pressure (MAP) < 65 mmHg or a systolic arterial pressure (SAP) < 90 mmHg, or the use of vasopressors to keep MAP ≥ 65 mmHg or SAP ≥ 90 mmHg, IF any of these conditions persist for 4 hours or more.

**NOTE**: Patients who received transiently vasopressors only during initial resuscitation (volume deficit) or had an iatrogenic-induced hypotension (e.g. intubation, bolus sedation), but are free of vasopressors and have no hypotension for at least two hours after initial resuscitation or the
hypotensive event, are defined to be not in shock. It is essential that at the
time of allocation of study medication, patients **MAY NOT** be in septic
shock.

**Adequate volume status** is defined as a central venous pressure ≥ 8
mmHg in non-ventilated and ≥ 12 mmHg in ventilated patients, and a
central venous oxygen saturation ≥ 70 %.

**Vasopressors** are defined as ≥ 5 μg/kg/min dopamine or any dose of
epinephrine, norepinephrine, vasopressin, or other vasopressor.

II. Patients with known hypersensitivity to hydrocortison-21-
hydrogensuccinate, natrium-monohydrogenphosphate , or mannitol
(placebo).

III. Patients who have a glucocorticoid history AND in whom a
continued glucocorticoid therapy may be indicated (e.g. > 10 mg
prednisolone equivalent per day for at least 5 days within the last 3
months). Topical or inhaled glucocorticoids are **NO** exclusion
criteria, unless there is an indication for continued systemic
glucocorticoid administration.

IV. Other indications for systemic glucocorticoid therapy (e.g. asthma,
COPD, anaphylaxis, autoimmune diseases)

V. DNR-order

VI. Moribund patients

VII. Pregnancy (positive pregnancy test in women with child bearing
potential)

VIII. Breast feeding women

IX. Age < 18 years

X. Concomitant or previous (within the last 30 days) participation in an
other interventional clinical trial

XI. Relationship to the investigator (e.g. relatives, colleagues, staff)

**Trial Design**

Placebo-controlled, randomised, double-blind multi-center study

**Primary Objective**

To investigate whether the application of low dose hydrocortisone (**ldHC**)
prevents within 14 days the progression to septic shock in patients with
severe sepsis who are not in shock.

**Secondary Objectives**

The study investigates whether the application of low dose hydrocortisone
affects:

- Mortality and survival
- Length of ICU and hospital stay
- The time until septic shock develops
- Organ dysfunctions
- Duration of mechanical ventilation
- Duration of renal replacement therapy
- Incidence of delirium
- The incidence side effects and adverse events (safety)
- Post Traumatic Stress Disorder and Health-related Quality of Life
- Adhesion molecule expression, monocyte function, Th1/Th2-ratio,
nitric oxide production in a subgroup of patients (Berlin sites)
- The host response to infection at the genomic, transcriptional, and
protein level (100 patients)

Further objectives:

- Assessment of the incidence of adrenal insufficiency at baseline
  and differences in the responses to hydrocortisone (at least 100
  patients)
- Continuation of the SepNet central blood sample storage bank for
identification and validation of future biomarkers of sepsis and evaluation of genetic polymorphisms (serum, plasma, DNA).

**Intervention**  
Trial intervention: 50 mg HC followed by an infusion of 200 mg HC/d for 5 days, 100 mg/d for 2 days, 50 mg/d for 2 days, and 25 mg/d for 2 days.  
Control intervention: Placebo  
Duration of intervention per patient: 11 days

**Primary endpoint**  
Septic shock within 14 days

**Secondary endpoints/ outcome(s)**
- 28-day mortality (proportion of patients who die within 28 days from any cause)
- 90 and 180-day mortality
- ICU-mortality
- Hospital mortality
- Time to death from any cause and sepsis-related death
- Length of ICU stay
- Length of hospital stay
- Time to septic shock and/or death within 14 days
- Frequency and duration of mechanical ventilation until ICU discharge
- Frequency and duration of renal replacement until ICU discharge
- Mean total SOFA (organ dysfunction) and mean SOFA subscores until ICU discharge but day 14 at maximum
- Frequency of weaning failure until ICU-discharge
- Frequency and severity of muscle weakness until ICU-discharge
- Frequency of GI-bleeding within 28 days
- Frequency of secondary infections within 28 days
- Frequency of delirium until ICU-discharge
- Blood sodium level and frequency of hyponatremia (> 155 mmol/l) within 14 days
- Blood glucose level and frequency of hyperglycemia (> 150 mg/dl) within 14 days
- Other AEs or SAEs within 28 days

**Sample size**  
380 total (190 per arm) (alpha=0.05; Power=0.8; two-sided test for proportions with continuity correction; \( \pi_{\text{Control}} = 0.4; \pi_{\text{Treatment}} = 0.25 \); allocation ratio 1:1; group sequential plan with O'Brien-Fleming alpha spending function and 3 looks) including 10% drop-out rate

**Biometry**  
**Primary Endpoint:** Two-sided comparison of septic shock rate in control group \( \pi_{\text{Control}} \) with treatment group \( \pi_{\text{Treatment}} \) using Chi-Square test in ITT population \( H_0: \pi_{\text{Control}} = \pi_{\text{Treatment}} \); \( HA: \pi_{\text{Control}} \neq \pi_{\text{Treatment}} \)  
**Interim-Analyses:** Two interim analyses at 1/3 and 2/3 of target sample size (group sequential plan with O'Brien-Fleming stopping boundaries).

**Trial sites**  
38 sites in Germany

**Trial duration**  
**Patient:** Treatment period 14 days, follow-up until day 28 or hospital discharge, follow-up 6 months after randomisation and 6 months after hospital discharge for PTSD/HrQoL  
**Trial:** Recruitment period is 3 years, total duration of trial is 4 years.
# Schedule of Assessments and Procedures I

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Pretreatment</th>
<th>Treatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 - -48 h</td>
<td>- 24 h</td>
<td>28 ICU-</td>
</tr>
<tr>
<td></td>
<td>1 2 3 4 5 6 7 8 9 10 11 12 13 14</td>
<td></td>
<td>Discharge</td>
</tr>
<tr>
<td></td>
<td>90 180</td>
<td></td>
<td>Hospital-</td>
</tr>
<tr>
<td>Time / Day</td>
<td>Severe Sepsis</td>
<td>Baseline</td>
<td>Discharge</td>
</tr>
<tr>
<td><strong>Assessment / Procedure</strong></td>
<td></td>
<td>Follow-up</td>
<td></td>
</tr>
<tr>
<td>Informed Consent</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Randomisation</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical / Surgical history</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concomitant medication</td>
<td>x</td>
<td>x x x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Etomidate- / GC-history</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source of infection</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA / GCS Score</td>
<td>x</td>
<td>x x x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>CAM-ICU, RASS</td>
<td>x</td>
<td>x x x x x x x x x x x x x x x x</td>
<td>x x</td>
</tr>
<tr>
<td>SAPS II / III, APACHE II</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH-test</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug accountability</td>
<td>x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin requirement</td>
<td>x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuresis</td>
<td>x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC, FFP, Colloids, Cristalloids</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total fluid intake</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catecholamines/Vasopressors</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP, MAP, DAP, ScvO2, CVP</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2, PCO2, BE, Lactate, pH</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO2/FIO2, PEEP, VT,Pplat</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp. heart rate, resp. rate</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics &lt; 1 h</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood cultures</td>
<td>x x x x x x x x x x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* within first 6 hours after diagnosis of severe sepsis
# Schedule of Assessments and Procedures II

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Pretreatment</th>
<th>Treatment</th>
<th>Posttreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Time / Day</td>
<td>ICU-Discharge</td>
<td>Hospital-Discharge</td>
<td>90</td>
</tr>
<tr>
<td>Assessment / Procedure</td>
<td></td>
<td></td>
<td>28</td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic shock</td>
<td>x x x x x x x</td>
<td>x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days ICU</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days Hospital</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days MV</td>
<td>x x x x x x x x x x x</td>
<td>x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Days renal support</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HrQoL, PTSD</td>
<td>x</td>
<td></td>
<td>x²</td>
</tr>
<tr>
<td>Safety</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Events</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary Infection</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Muscle Weakness (MRC Score)</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Weaning Failure</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Hypernatremia (&gt;155 mmol/l)</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia (&gt;150 mg/dl)</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>GI-Bleeding</td>
<td>x x x x x x x x x x x x x x x</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
</tr>
<tr>
<td>Blood samples and values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine blood values (local routine laboratory chart data)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, Creatinine, Urea, Platelets, Hb, PT, PCO₂, PaO₂, ALT, AST,</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyr, LDH, Bilirubin, Na, K,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP, PCT, Lactate, pH, Leukocytes, etc.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study specific blood samples</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SepNet Sample Bank (DNA)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SepNet Sample Bank (Serum, Plasma)</td>
<td>x x x x x x x x x x x x x x x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaxGene tube (RNA)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>EDTA Serum (only Berlin sites)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Cortisol (serum)</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 1 x after additional informed consent
* 2 months after hospital discharge
* 6 months after hospital discharge
1 RATIONALE

1.1 Medical Background

Severe sepsis and multiple organ dysfunction are amongst the leading causes of death in intensive care units (ICUs). The German Competence Network Sepsis (SepNet) prospective cross-sectional prevalence study revealed a prevalence of severe sepsis/septic shock of 11% in 3877 screened patients in 454 ICUs [BRUNKHORST 2005]. The incidence of severe sepsis/septic shock was estimated as 75,000 cases per year (110 per 100,000 inhabitants), comparable with the incidence of acute myocardial infarction (143/100,000). With an estimated 40,000 deaths per year, severe sepsis/septic shock is the third most frequent cause of death in Germany after coronary artery disease and acute myocardial infarction. Estimated additional costs in Germany for treatment of severe sepsis/septic shock are about 23,000 € per patient, corresponding to 1.1 -2.4 billion € per year, or 21% to 46% of all costs for ICU therapy [MOERER 2002]. Despite tremendous progress in ICU therapy, mortality of septic shock changed only little from about 60% in the 50s to 40-50% in 2002 [DELLINGER 2003], and was 54% in the SepNet prevalence study. The risk of death correlates with co-morbidities and the occurrence of organ dysfunction. It is critical that development of cardiovascular failure is the most serious and independent risk factor for death [ALBERTI 2003]. The relative risk of dying increases from 1.53 (95% CI, 1.26 -1.86; p < 0.0001) to 2.64 (95% CI, 2.21-3.15; p < 0.0001) in patients with severe sepsis and septic shock, respectively.

Standard intensive care of patients with severe sepsis and septic shock include surgical treatment of septic foci, antibiotic therapy, hemodynamic stabilization, and general measures such as lung protective mechanical ventilation, glycemic control, enteral nutrition, and others. There is evidence that early hemodynamic stabilization (Early Goal Directed Therapy, EGDT) within the first hours of severe sepsis is critical and improves outcome [RIVERS 2001]. However, there is no established or specific therapy to prevent development of cardiovascular failure.

During the last decade low doses of hydrocortisone (ldHC) have been investigated as an adjunctive treatment for hemodynamic stabilization in patients with volume resistant septic shock. There is strong evidence from a meta-analysis that treatment with ldHC (200-300 mg/day) for 5-7 days in patients with septic shock significantly reduces the relative risk of dying (RR: 0.8; 95% CI: 0.67-0.95; p = 0.01) and reverses shock (RR: 1.6; 95% CI: 1.27-2.03; p < 0.0001 [ANNANE 2004b]. Some data indicate that ldHC is more effective in patients with relative adrenal insufficiency (RAI) [OPPERT 2005,ANNANE 2002], but it is controversially debated how to define RAI and whether efficacy depends on RAI [MINNECI 2004,KEH 2004]. The EU-funded
multinational CORTICUS study investigated the efficacy and safety of \( ldHC \) in 499 patients with septic shock [SPRUNG 2008]. Data from this study indicate that the diagnosis of RAI may be biased by between-assay variations of cortisol measurement, and that in patients with septic shock but not in healthy control samples, commercial test assays overestimate total cortisol values. Thus, the role of adrenal function tests in septic shock patients remains to be established. There are only limited data available of RAI in patients with severe sepsis without shock. In the CORTICUS trial, \( ldHC \) did not improve survival and mortality, but significantly reversed shock independent from adrenal function confirming hemodynamic effects of hydrocortisone. It has to be stressed that patients in this study had less severe shock than in the study by Annane and that the time window for application of study drug was longer (8 versus 72 h). Taking into account these recent results, the Surviving Sepsis Campaign guidelines 2008 suggest to treat adult patients with septic shock only after blood pressure is identified to be poorly responsive to fluid resuscitation and vasopressor therapy [DELLINGER 2008]. It is relevant that treatment of severe sepsis with a combination of antibiotics and < 1000 mg HC per day was already propagated in the 50s and 60s. In a systemic review, 13 out of 20 studies in patients with severe sepsis showed positive effects of treatment with < 1000 mg HC, however, the study designs had been too poor to draw any final conclusions [WEITZMAN 1974]. With the change of the pathophysiological model in the 60s, away from adrenal insufficiency towards inhibition of inflammation, there was no longer need to restrict the dosage of glucocorticoids, and to avoid side effects, the duration of treatment was shortened to one or two days. Two major studies in the 80s yielded no reduction of mortality, prevention or resolution of shock, but an increased risk for secondary infections [BONE 1987, SPRUNG 1984]. With the next change of paradigm, the reintroduction of RAI into septic shock pathophysiology in the 90s, \( ldHC \) was only investigated in patients with shock. The Surviving Sepsis Campaign (SSC) guidelines recommend \( ldHC \) only in patients with septic shock due to lack of evidence in patients with severe sepsis who are not in shock [KEH 2004].

In a recent randomised controlled trial in 46 patients with community acquired pneumonia (CAP), therapy with \( ldHC \) (10 mg/h for 7 days) was effective in patients with severe sepsis without shock [CONFALONIERI 2005]. Hospital mortality was 0% with \( ldHC \) and 30 % in the placebo group (p = 0.009); length of ICU and hospital stay, and days of mechanical ventilation were significantly lower. Importantly, none of the patients treated with \( ldHC \) developed septic shock, but 52 % of patients treated with placebo (odds ratio 0.03, 95% CI, 0.00015-0.51, p = 0.0005).

Taken together, there is strong evidence that development of shock is one of the most important risk factors of death. Prevention of shock development may be a promising approach to improve outcome.
1.2 Hypothesis and Novel Aspects of the Trial

The hypothesis is that treatment with low doses of hydrocortisone prevents the progression to septic shock in patients with severe sepsis. We postulate that early inhibition of an aggravated inflammatory response affect key mediators which are involved in development of shock and organ dysfunction.

There is strong evidence that \textit{ld}HC suppresses the production of cytokine-induced nitric oxide (NO) formation by the inducible nitric oxide synthase (iNOS) \cite{KEH_2003}. NO is a central mediator in sepsis pathophysiology and is involved in septic cardiomyopathy, maldistribution of blood flow, cytopathic hypoxia, and vasodilation \cite{VINCENT_2000,BREALEY_2002}. Recent data indicate that endothelial dysfunction and decreased production of endothelial NO by the endothelial (e)NOS contributes to microcirculatory failure in septic shock \cite{DE_BACKER_2002}. This is in accordance with the observation from a randomised controlled trial, that inhibition of eNOS by an unselective NO-inhibitor is harmful \cite{LOPEZ_2004}. However, glucocorticoids only inhibit iNOS but not eNOS \cite{RADOMSKI_1990}. There is rather evidence that glucocorticoids may induce eNOS-activity by a non-transcriptional mechanism \cite{LIMBOURG_2002,HAFEZI-MOGHADAM_2002}. Indeed, a recent pilot-study indicates, that in patients with septic shock, application of \textit{ld}HC improves microcirculatory blood flow \cite{BUCHELE_2006}. Taken together, early inhibition of aggravated NO-formation may be protective with regard to the development of shock and other organ dysfunctions. Since \textit{ld}HC has been proven to reverse shock, one might speculate that \textit{ld}HC should also be effective to prevent progression to shock. It is obvious, that in the complex scenario of sepsis and multi-organ dysfunction, inhibition of iNOS is only one explanatory example how \textit{ld}HC may be protective. It is the unique property of glucocorticoids to interact with the central transcription factor NF-\textit{kB} which is involved in the production of multiple cytokines, chemokines, and adhesion molecules, and which plays a mayor role in the development of organ dysfunction in severe sepsis and septic shock \cite{BOHRER_1997}.

Protective effects of \textit{ld}HC on shock development have not been investigated prospectively. The intend of the study is to confirm the encouraging data reported for patients with CAP, and to proof efficacy and safety in a broader spectrum of patients with severe sepsis due to community and hospital acquired pneumonia, abdominal sepsis, or other origin.

HYPRESS is a randomised placebo-controlled study to investigate the efficacy and safety of \textit{ld}HC to prevent the development of septic shock in patients with severe sepsis. A total of 380 patients will be enrolled in centers of the German SepNet trial platform and in non-SepNet centers of the Berlin Vivantes Clinical Network. The primary endpoint in HYPRESS is sepsis-induced hypotension (septic shock) within 14 days. Patients may receive \textit{ld}HC when septic shock develops. Thus, standard intensive care according to the recommendations of the German Sepsis Society and the Surviving Sepsis Campaign is not withheld from patients.
Results of this study may have important impact on daily clinical practice and treatment guidelines.

1.3 Special Aspects of HYPRESS

1.3.1 Study drug administration, dosage, dosage regimen, and treatment duration.

Patients are randomised to receive either placebo or \textit{ld}HC at a dosage of 200 mg per day for 5 days per continuous infusion; afterwards the study medication is tapered in three steps until day 11. The DSG and SSC recommend either bolus or continuous application in patient with septic shock [KEH 2004]. However, bolus application of \textit{ld}HC may complicate glycemic control and significant increases of blood glucose above 150 mg/dl after bolus application of 50 mg HC and undulation of blood glucose during bolus application have been described [LOISA 2007,WEBER-CARSTENS 2007b,WEBER-CARSTENS 2007a]. Thus, in HYPRESS HC is administered by a continuous regime and the study medication is tapered over several days to avoid hemodynamic and immunologic rebound effects after abrupt cessation, which have been described in patients with septic shock [KEH 2003]. The daily dose of HC administration, tapering regime and duration of treatment has been adapted to that of the CORTICUS trial. The regime of continuous infusion is preceded by a single bolus of 50 mg \textit{ld}HC or placebo as a loading dose, which is the same dose used in the CORTICUS trial (repetitive bolus application) and lower than doses in other studies which used three times a day 100 mg of HC in a bolus regime, or used 100 mg HC as a single loading dose followed by a continuous infusion [MINNECI 2004]. The maximum total amount of HC the patient receives is 250 mg HC on day 1, which is within the recommended range of 200-300 mg HC per day for patients with septic shock [REINHART 2006,DELLINGER 2004].

1.3.2 Adrenal insufficiency

Adrenal function has predominantly been investigated in patients who are in septic shock. There is an ongoing discussion how to define adrenal insufficiency in septic shock; however, there is consensus that cortisol deficiency plays a major role [ANNANE 2000,MATOT 1998,KEH 2004]. Based on the current data, adrenal insufficiency may be best defined as a cortisol increase of $\leq 9 \, \mu g/dl$ or a basal cortisol $< 15 \, \mu g/dl$ [COOPER 2003]. This is in accordance with a retrospective data analysis in 477 patients, which is part of the retrospective CORTICUS study. There is evidence from this retrospective analysis, that patients with severe sepsis have a significantly lower incidence of adrenal insufficiency than patients with septic shock [LIPINER-FRIEDMAN 2007].
In HYPRESS, adrenal function will be investigated by a short ACTH-test at baseline. The results may give important information about the incidence of adrenal insufficiency in patients with severe sepsis. Another important issue is, whether efficacy of \textit{id}HC therapy in severe sepsis depends on adrenal function. If it comes out that \textit{id}HC prevents septic shock irrespective of adrenal function, which is expected, the value of adrenal function tests in patients severe sepsis who are not in shock has to be questioned. The cortisol measurements will be performed in a reference laboratory to avoid bias due to variation of different test assays (for detail see chapter 12).

1.3.3 Posttraumatic stress syndrome (PTSD) and health-related quality of life (HrQoL)

PTSD is a stress-related psychiatric disorder that may occur after critical illness. PTSD is frequently associated with a compromised HrQoL. It is estimated that about 39 % of patients with septic shock suffer from PTSD and impaired HrQoL [SCHELLING 1999]. There is evidence that \textit{id}HC may be protective for development of PTSD (for details see chapter 9). In HYPRESS, a panel of related questionnaires will be performed at hospital discharge and 6 months after hospital discharge. This is the first time that this important question is prospectively evaluated in a randomised trial in patients with severe sepsis who receive \textit{id}HC.

1.3.4 Immunomonitoring

Glucocorticoids play an essential role in the host response to stress [FRANCHIMONT 2003]. Activation of the adrenal axis and release of cortisol attenuates the inflammatory response and protects the organism from damage. In sepsis, the increased production of pro-inflammatory mediators may induce organ damage, but on the other hand, a profound anti-inflammatory response may be harmful either, and accompanied by immunoparalysis [MUNFORD 2001]. There is increasing evidence that the balance between inflammation and anti-inflammation is disturbed, and that in severe sepsis or septic shock there is an increased activation of NF-\kappaB. NF-\kappaB is one of the most important transcription factors, which is involved in innate and adaptive immunity. Cortisol effects are mediated by glucocorticoids receptors (GR), which inhibit NF-\kappaB. One current concept is that during systemic inflammation, NF-\kappaB-driven pathways overrule GR-driven pathways, and that application of \textit{id}HC may restore the balance [FRANCHIMONT 2003]. Gene expression analysis in healthy donor mononuclear revealed that low doses of steroids rather stimulate innate immune responses and suppress the adaptive immunity [GALON 2002]. In animal experiments, the addition of glucocorticoids to antibiotic treatment increased the LD$_{50}$ of gram-positive and gram-negative pathogens [SILVERSTEIN 2003]. Furthermore, exposure of human monocytes to methyl-prednisolone enhanced bacterial killing in a dose-dependent manner [MEDURI 2001]. Taken together, there is evidence that glucocorticoids play a role in the
first line of defense. However, glucocorticoids are known to inhibit adaptive immunity and may induce proliferation of TH-2 cells and downregulate the expression of HLA-DR receptors on monocytes. In patients with septic shock, application of ldHC for three days was accompanied with rather immunomodulatory effects and did not induce aggravated immunosuppression [KEH 2003]. Both, pro-inflammatory (e.g. interleukin 8 and 6) and anti-inflammatory mediators (interleukin 10 and tumor necrosis factor receptors) were significantly depressed, whereas other inflammatory cytokines such as interleukin 12 and interferon-γ rather increased. Furthermore, already low HLA-DR expression on monocytes was not further depressed by ldHC. A recent study indicates, that ldHC in septic shock has anti-inflammatory effects but does not promote the synthesis of anti-inflammatory mediators [OPPERT 2005]. Immunologic effects of prolonged treatment with low doses of hydrocortisone in patients with severe sepsis who are not in shock have not been investigated. Immunological data in HYPRESS will be obtained in a pilot-study in selected centers in Berlin (see scientific add-on projects chapter 9).

HYPRESS will be the first controlled study of ldHC, which investigates the host response to ldHC in severe sepsis at the genetic, transcriptional, and protein level. This important add-on project will be performed in 100 patients in selected sites, and will gain essential information about immune effects of glucocorticoids in severe infections (see scientific add-on projects chapter 9).

1.4 Risk-Benefit Consideration

Possible risks associated with ldHC

Based on current available data, there is no evidence that treatment with ldHC is associated with severe harmful side effects. However, there are some important issues to be addressed. Almost all data on side effects are derived from studies in patients with septic shock. In one study an increase of sodium (> 155 mmol/L) and alanine amino transferase was reported [BRIEGEL 1999]. A meta-analysis pointed out, that overall there had been no increased risk for gastrointestinal bleeding, super-infections, or hyperglycemia with the use of ldHC [ANNANE 2004a]. Glucocorticoids are in use for more than 50 years for different diseases. Although there are a large number of possible harmful effects, such as osteoporosis or development of ulcers, these complications have been exclusively observed during prolonged treatment. It is not expected that yet unknown serious adverse drug reactions occur during treatment with ldHC over several days.
With regard to hyperglycemia, it is important to recognize that the concept of intensive insulin therapy was implicated into clinical practice only recently [VAN DEN BERGHE 2001]. The German Sepsis Society (GSS) recommends keeping blood glucose below 150 mg/dl, since tight glycemic control aiming to achieve physiologically normal blood glucose values (80-110 mg/dl) may be associated with an increased risk of hypoglycemia; additionally, most of the data of tight glycemic control have been derived from critically patients without sepsis. The recently finished VISEP-study of the German SepNet indicates that in patients with severe sepsis or septic shock, the risk of hypoglycemia during tight glycemic control outweighs beneficial effects (personal communication Dr. F. Brunkhorst, SepNet). However, glucocorticoids may rather induce hyperglycemia and thus may complicate the glycemic control strategy. This may especially be the case, when $ldHC$ is administered in a repetitive bolus regime. Indeed, in an observational study, we observed a significant increase of blood glucose above 150 mg/dl after 50 mg hydrocortisone application, whereas during a continuous application hydrocortisone, blood glucose was constantly below 150 mg/dl [WEBER-CARSTENS 2007a]. Based on these data, and the general practice in Germany, hydrocortisone will be administered as a continuous infusion in the HYPRESS study.

Secondary infections have only been reported in studies in which patients with severe sepsis or septic shock have been treated with high doses of steroids. There had been an increased time of resolution of secondary infections and an increased mortality from these infections [MINNECI 2004]. A recent study showed a significantly higher risk of cytomegalie virus infection in critically ill patients with fever not due to bacteriemic or fungal origin, who received steroids. However, the duration and dosage of glucocorticoid application was not reported in this study [JABER 2005]. It is generally assumed that high doses of glucocorticoids induced a profound immunosuppression. Studies with $ldHC$ do not report an increased risk of secondary infections. In one study, the incidence of wound infections was significantly lower in the group which received $ldHC$ than in the control group [ANNANE 2002]. In the placebo controlled late ARDS NIH-network trial, treatment with 2 mg/kg methylprednisolone for 14 days was not associated with an increased rate of infectious complications [STEINBERG 2006]. In contrast, preliminary data from the CORTICUS study indicate an increased number of secondary infections in patients treated with $ldHC$, but the difference between treatment groups was not statistically significant. Thus, it remains uncertain whether the use of $ldHC$ is associated with an increased risk of secondary infections. Immunological data indicate that $ldHC$ does not induce immunosuppression, but rather acts as an immunomodulator and inhibits both pro- and anti-inflammatory mediators [KEH 2003,OPPERT 2005]. Since secondary infections are a very important safety issue, patients will be closely monitored for secondary infections in HYPRESS.
Treatment with glucocorticoids is a risk factor for development of muscle weakness in the ICU [DE JONGHE 2002, HERRIDGE 2003]. Muscle weakness is the major contributing factor for weaning failure [DE JONGHE 2004a]. However, the currently available data do not distinguish between low and high dose glucocorticoid administration and the duration of treatment; patients with muscle weakness often had a glucocorticoid history and received higher than ldHC doses. It is well known that high doses of glucocorticoids may induce critical illness related myopathy/polyneuropathy (CIM/CIP), especially in combination with non-deporalizing muscle relaxants. It is unknown whether this is also the case for ldHC. Interestingly, in patients with weaning failure who had a cortisol deficiency, ldHC significantly improved weaning from mechanical ventilation [HUANG 2006]. A reasonable hypothesis is that CIM/CIP occurs early in the course of sepsis, and that inflammation is a major contributing factor. The incidence CIM/CIP has been reported to be as high as 20-50% in patients with systemic inflammation [BOLTON 2005]. Thus, inhibition of inflammation early in the course of severe sepsis may even have positive effects on CIM/CIP. Indeed, in the study with ldHC for CAP, none of the patients who received ldHC and 13% of patients in the control group developed CIM/CIP (not significant) [CONFALONIERI 2005]. In contrast, patients who received 500-1000 mg hydrocortisone equivalent for late (> 14 days) acute respiratory distress syndrome had a significantly higher incidence of muscle weakness and weaning failure [STEINBERG 2006]. Muscle weakness is a very important secondary endpoint in HYPRESS, and patients will be monitored during the study.

Risks associated with the ACTH-test (250 μg cosyntropin) are minimal. Very rarely, hypersensitivity reactions have been reported, but not in recent studies where adrenal function was tested in patients with sepsis. However, patients are under continuous clinical and hemodynamic monitoring according to standard intensive care practice. Obtaining blood samples for study-specific scientific projects is associated with no additional risk, since blood is drawn from already placed intravenous catheters, which is standard practice for treatment of patients with severe sepsis. The total amount of drawn blood is about 190 ml within 7 days, the maximum daily amount is about 35 ml at baseline. This amount of blood sampling is medically irrelevant. Thus, blood sampling within the study is a justifiable burden for patients included into HYPRESS.

Possible benefits associated with participation in the study and treatment with ldHC

The application of study medication is an add-on therapy (adjunctive treatment), i.e. all patients receive standard intensive care therapy, and no established or recommended therapy is withheld from patients. All participating centers have to commit to treat patients according to the S2-guidelines of the German Sepsis Society [REINHART 2006], which are based on the
guidelines of the Surviving Sepsis Campaign [DELLINGER 2004]. Implementation of the guidelines in clinical practice have shown to reduce morbidity, mortality, and costs in patients with severe sepsis and septic shock [GAO 2005]. Participation in the trial may increase the awareness for the implementation of S2-guidelines in clinical practice.

For patients treated with \textit{ldHC}, there is the possible benefit that development of septic shock is prevented. This may be associated with a reduction of other organ dysfunctions and probably death. For patients who receive placebo, there is no additional risk.

There is also the hypothesis, that \textit{ldHC} may improve the immune response to infections (see above). To prove this hypothesis, immunomonitoring is an essential part of this study. For the group of patients with severe sepsis, results of this study may have considerable impact on daily clinical practice in ICUs. The group of patients will definitely profit from any study results. The study contributes to answer the pivotal question whether septic patients without shock should be treated with \textit{ldHC}. If it can be confirmed that \textit{ldHC} is effective to prevent shock in patients with severe sepsis without increasing the risk of severe harmful effects, a large mixed population of patients with a high risk of death may profit from this adjunctive treatment. However, if \textit{ldHC} turns out to be ineffective to prevent shock or even to be harmful, this would be a very important result as well, and may restrict widespread use of \textit{ldHC} only to proven indications. Lastly, hydrocortisone is inexpensive and available everywhere, hence cost-effectiveness may reduce health-care resources.

\textbf{Risk-benefit consideration}

- For the individual patient, there is no or only minimal risk. No standard therapy will be withheld from any patient. In patients who develop septic shock, the study medication is withdrawn and may be replaced by \textit{ldHC}, at the discretion of the investigator. For patients in both groups, additional blood sampling is a justifiable burden without medical risk. Patients who receive verum may profit from prevention of septic shock.
- Patients may profit from further implementation of S2-guidelines in clinical practice.
- Patients may profit from diagnosis of posttraumatic stress disorder.
- For the group of patients with severe sepsis, results of this study will have definite impact on future therapeutic recommendations. Thus, the whole group of patients will profit from this study.
- Since hydrocortisone is cheap and available everywhere the reduction of costs may have impact on health-care resources.
- Ethically, the study is justifiable, since there is no or only minimal risk for the individual patient, but a possible benefit for patients who receive verum, and a benefit for the group of patients with severe sepsis.
2 OBJECTIVES

2.1 Assessment of efficacy and safety

Efficacy of IdHC application will be assessed by the primary objective, i.e. prevention of septic shock (see 2.2). Secondary efficacy criteria are effects on mortality and survival, length of stay in the ICU or hospital, the time until development of septic shock, duration of mechanical ventilation, duration of renal support, and progression and/or regression of inflammation and organ dysfunctions (see 2.3). Assessment of inflammation and organ dysfunctions are performed by scores (SOFA, CAM-ICU, RASS), and the devolution of routinely obtained laboratory, hemodynamic, and organ function parameters: ventilation and lung function (PaO₂, PaCO₂, PEEP, VT, Pplat, FiO₂, respiratory rate), oxygen transport capacity (O₂-saturation, hemoglobin), macrocirculation (arterial blood pressure, CVP, use of catecholamines and vasopressors, fluid intake), microcirculation (lactate, base excess, pH), liver function (bilirubin, ASAT), coagulation (platelet count, D-Dimer, PT,), kidney function (creatinine, urea, diuresis), and systemic inflammation and infection (leukocytes, temperature, CRP, PCT). Additional efficacy criteria are derived from the devolution of study specific immune parameters in subgroups of patients such as the production of nitric oxide and effects of IdHC on the transcriptomic and proteomic response (for details see 1.3.4, 9.2, 9.3), and the assessment of possible long term effects such as PTSD and HrQoL (see 9.1).

Assessment of safety of IdHC application is performed by documentation of adverse events not related to the underlying disease (sepsis) (for details see 7). Of special interest are possible side effects of glucocorticoids such as the occurrence of secondary infections, muscle weakness and weaning failure, gastrointestinal bleeding, hyperglycemia, and hypernatremia. For a detailed description for safety criteria see 7.1.2. Assessment of safety is also derived from the devolution of routinely obtained laboratory parameters (e.g. liver enzymes). In addition, study specific immune parameters will be obtained in selected groups of patients which target specifically on immunosuppression such as the expression of HLA-DR on monocytes, the balance between TH1 and TH2 T-lymphocytes, and the function of monocytes upon endotoxin stimulation (endotoxin tolerance), for a detailed description see 9.3. The latter is part of a scientific substudy and will not be recognized for adverse events reporting, since interpretation of the results for the group of patients will only be possible after unblinding.
2.2 Primary Objectives

The primary objective of this study is to investigate whether the application of low dose hydrocortisone prevents within 14 days the progression to septic shock in patients with severe sepsis who are not in shock.

For a detailed definition of septic shock see appendix.

2.3 Secondary Objectives

The study investigates whether the application of low dose hydrocortisone affects:

- Mortality and survival
- Length of ICU and hospital stay
- The time until septic shock develops
- Organ dysfunctions
- Duration of mechanical ventilation or continuous positive airway pressure
- Assessment of delirium
- Duration of renal replacement therapy
- Incidence of side effects and adverse events (safety)
- Post Traumatic Stress Disorder and Health-related Quality of Life
- Adhesion molecule expression, monocyte function, Th1/Th2-ratio, nitric oxide production in a subgroup of patients (Berlin sites)
- The host response to infection at the genomic, transcriptional, and protein level (100 patients)

Further objectives:

- Assessment of the incidence of adrenal insufficiency at baseline and differences in the responses to hydrocortisone (at least 100 patients)
- Continuation of the SepNet central blood sample storage bank for identification and validation of future biomarkers of sepsis and evaluation of genetic polymorphisms (serum, plasma, DNA).
3 TRIAL DESIGN AND DESCRIPTION

3.1 Trial Design

HYPRESS is designed as a double-blind, placebo-controlled, randomised, phase-III, two-armed, parallel-group, multi-centre trial (see flow chart).

3.2 Requirements for Participating Investigators and Trial Sites

The trial is performed in centers which are integrated into the German SepNet clinical trial platform. Associated centers may participate if they meet the requirements for conducting the trial, i.e. the principal investigator and the ICU staff have to be familiar in treating critically ill patients with severe sepsis and septic shock regularly. All participating centers have to commit to treat patients according to the S2-guidelines of the German Sepsis Society (DSG) and German Interdisciplinary Association of Critical Care Medicine (DIVI) [REINHART 2006]. Additional requirements for conducting the study include the facility for preparation and storage of blood samples (cooled centrifuge and a deep freezer [– 18-20 °C]), and a PC with HTTPS access to the internet (Internet Explorer 6.0 or higher).

The investigators will be trained in different ways. First, investigators will receive all necessary material for conducting the trial (Investigator Site File and working instructions). Second, a central meeting will take place before the study begins. Third, investigators will be trained at the KKSLS in small groups for the eCRF and trial specific procedures. All centers will have an initiation-visit.

3.3 Trial Sites and Number of Trial Subjects

A total of 380 patients will be enrolled in the study. It is assumed that all centers will be able to recruit at least 4-5 patients per year, on the average. The study is performed in 38 centers in Germany. Thirty-one sites belong to the SepNet trial platform of which two are also centers of the VIVANTES Clinical Network Berlin, additional six centers of the VIVANTES Clinical Network Berlin and four not affiliated centers participate. See appendix for list of participating sites.
3.4 Expected Duration of Trial

Duration of the trial per patient

Duration of the whole trial

<table>
<thead>
<tr>
<th>Month 1-6</th>
<th>7-24</th>
<th>25-36</th>
<th>37-48</th>
</tr>
</thead>
<tbody>
<tr>
<td>BfArM, EC, ISF, Study medication production /shipping Investigator meeting/visits Logistics, eCRF, monitoring plan, SOPs, AE database, Statistical plan</td>
<td>Recruitment (36 m)</td>
<td>Follow-up</td>
<td>Data management, Queries, Safety Monitoring</td>
</tr>
<tr>
<td></td>
<td>Interims A.</td>
<td>Interims A.</td>
<td>Database closure, Biometry, final Analysis, Report, Preparation of scientific presentations and publications (&gt; 48m)</td>
</tr>
</tbody>
</table>

The total duration of the trial is 48 months (see figure above). The recruitment period is 36 months. WP: work package.

Follow-up and PTSD questionnaire:

Follow-up for PTSD and HRQoL is excluded from interims and final analyses, since questionnaires after 6 months may delay data analysis. The analysis of PTSD will be performed separately in a blinded fashion.

3.5 Premature Termination

3.5.1 Premature closure of a trial site

Premature closure of a trial site is to be considered if:

- it does not meet the technical requirements of the protocol,
- the conduct of the study is not compliant with the protocol,
- the data quality is not sufficient,
- the recruitment is not sufficient.

The premature closure of a site will be decided by the scientific coordinator after consultation with the HYPRESS SepNet Steering Committee.
Investigators and trial sites deciding not to take part in the trial any longer have to inform the scientific coordinator immediately. The decision should be well-founded. Details on further treatment and follow-up of patients on study have to be discussed with the scientific coordinator.

3.5.2 Premature termination of the trial

In case of the following situations, a premature termination of the trial has to be considered:

- Serious adverse drug reactions / not justifiable toxicity
- Substantial changes in risk-benefit considerations
- New insights from other trials
- Insufficient recruitment rate
- Unsustainable trial organization

The Data Monitoring and Safety Board (DMSB) will monitor the study conduct and the safety aspects of the trial on a regular basis, and will give recommendations to the HYPRESS SepNet Steering Committee whether to stop the trial or to change the trial protocol. The sponsor will then decide, in agreement with the HYPRESS SepNet Steering Committee, on the actions to be taken.

According to the German drug law, the trial may be suspended or prematurely terminated by decision of the competent federal authority (Bundesinstitut für Arzneimittel und Medizinprodukte – BfArM).
4 SELECTION OF TRIAL SUBJECTS

4.1 Inclusion Criteria

Patients must meet ALL inclusion criteria:

1. Informed consent from patient, legal representative, proxy, or preliminary informed consent by independent medical consultant.

2. In women with child bearing potential an effective contraception with a failure rate < 1 % (for definition see below).

3. Clinical evidence of INFECTION (may be present ≥ 48 hours) –
   At least one of a-d is required.
   a. Pathogenic micro-organism in blood, sputum, urine, or normally sterile body fluid
   b. Identified focus of infection (e.g. ruptured bowel, purulent drainage or sputum)
   c. Presence of granulocytes in normally sterile body fluid
   d. Clinically suspected infection without positive culture of pathogenic microorganism (e.g. new infiltrate in chest X-ray, treated pneumonia, necrotizing fasciitis, purpura fulminans)

4. Evidence of SIRS (may be present ≥ 48 hours) –
   At least two of a-d are required.
   a. Fever (≥38 °C) or Hypothermia (≤ 36 °C)
   b. Tachycardia (≥ 90 bpm)
   c. Tachypnea (≥ 20 bpm) or hyperventilation (PaCO₂ ≤ 33 mmHg [≤ 4.3 kPa], or mechanical ventilation
   d. Leukocytosis (≥ 12.000 / μl) or leukopenia (≤ 4.000 / μl) or ≥ 10 % immature forms

5. Evidence of ORGAN DYSFUNCTION (may NOT be present ≥ 48 hours –
   At least one organ dysfunction of a-e is required
   a. Encephalopathy: Reduced vigilance, disorientation, agitation, delirium etc. in the absence of psychotropic drugs
   b. Acute renal dysfunction: Oliguria: ≤ 0.5 ml/kg/h ≥ 2 h despite adequate volume replacement and/or creatinine increase > 2 x above the normal upper range, and/or need for renal replacement therapy.
   c. Coagulation dysfunction: Platelets ≤ 100.000/μl or more than 30 % decrease from baseline within 24 hours. Thrombocytopenia may not be due to haemorrhage or immunologically induced.
   d. Pulmonary dysfunction/hypoxemia: PaO₂ ≤ 75 mmHg [≤ 10 kPa] at room air or PaO₂/FiO₂ ≤ 250 mmHg [≤ 33 kPa] with oxygen application. Hypoxemia may not be due to primary cardiac or pulmonary dysfunction (e.g. emphysema)
Microcirculatory dysfunction: Lactate > 1.5 x above the normal upper range and/or base deficit ≥ 5 mmol/l and/or metabolic acidosis with pH < 7.3 and/or depressed capillary refill/mottling and/or significant body edema (capillary leakage syndrome)

Definition of effective contraception:
A highly effective method of birth control is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner. For subjects using a hormonal contraceptive method, information regarding the product under evaluation and its potential effect on the contraceptive should be addressed [ICH-ORG 1995]

Due to the severity of the disease and hospitalisation, sexual abstinence during application of the study medication is assumed and may be regarded as an effective method of contraception, even if the investigator is not aware of an alternative mode of applied contraceptive method at the time of inclusion into the study.

4.2 Exclusion Criteria

Patients will be excluded for ANY ONE of the following reasons:

I. Sepsis-induced HYPOTENSION despite adequate volume replacement defined as a mean arterial pressure (MAP) < 65 mmHg or a systolic arterial pressure (SAP) < 90 mmHg, or the use of vasopressors to keep MAP ≥ 65 mmHg or SAP ≥ 90 mmHg, IF any of these conditions persist for 4 hours or more.

NOTE: Patients who received transiently vasopressors only during initial resuscitation (volume deficit) or had an iatrogenic-induced hypotension (e.g. intubation, bolus sedation), but are free of vasopressors and have no hypotension for at least two hours after initial resuscitation or the hypotensive event, are defined to be not in shock. It is essential that at the time of allocation of study medication, patients MAY NOT be in septic shock.

Adequate volume status is defined as a central venous pressure ≥ 8 mmHg in non-ventilated and ≥ 12 mmHg in ventilated patients, and a central venous oxygen saturation ≥ 70 %.

Additional information of volume status derived from extended monitoring (e.g. intra-thoracic blood volume index) will be documented in the eCRF.

Vasopressors are defined as ≥ 5 μg/kg/min dopamine or any dose of epinephrine, norepinephrine, vasopressin, or other vasodilator.
II. Patients with known hypersensitivity to hydrocortison-21-hydrogensuccinate, natrium-monoxygenphosphate, or mannitol (placebo).

III. Patients who have a glucocorticoid history AND in whom a continued glucocorticoid therapy may be indicated (e.g. > 10 mg prednisolone equivalent per day for at least 5 days within the last 3 months). Topical or inhaled glucocorticoids are NO exclusion criteria, unless there is an indication for continued systemic glucocorticoid administration.

IV. Other indications for systemic glucocorticoid therapy (e.g. asthma, COPD, anaphylaxis, autoimmune diseases)

V. DNR-order

VI. Moribund patients

VII. Pregnancy (positive pregnancy test in women with child bearing potential)

VIII. Breast feeding women

IX. Age < 18 years

X. Concomitant or previous (within the last 30 days) participation in an other interventional clinical trial

XI. Relationship to the investigator (e.g. relatives, colleagues, staff)

NOTE: The use of etomidate is no exclusion criteria. However, the use of etomidate is strongly discouraged in critically ill patients due to the known inhibitory effects on adrenal function and steroid production. The use of etomidate within 72 hours before inclusion time will be documented in the eCRF.

4.3 Reason for gender distribution (GCP-V §7 (2) Nr. 12)

There is evidence that male gender is associated with an increased risk for development of severe sepsis and mortality. It is therefore anticipated that more man than women will be included into the study (approximately 60:40). This gender distribution will be appropriate to recognise gender specific differences in response to idHC with regard to shock prevention and secondary outcomes.
5 INVESTIGATIONAL PRODUCT

5.1 Study Drug

The study medication is provided in vials.
1 vial verum contains a lyophilisate of 133.7 mg hydrocortisone-21-hydrogensuccinate-Na., which is equivalent to 100 mg hydrocortisone and natrium-monohydrogenphosphate (buffer).
1 vial placebo contains a lyophilisate of 133 mg mannitol.

Manufacturer:
BAG Health Care GmbH
Amtsgerichtsstraße 1-5
35423 Lich

5.2 Packaging and Labelling of the Study Drug

The investigational product will be manufactured by BAG Healthcare GmbH according to the standards of Good Manufacturing Practice (GMP). The study drug will be labelled as required by the ICH-GCP Guideline E6 and the German drug law (AMG §10). The HYPRESS-Study will be carried out in Germany, thus drug labels will be in German.

The study drug will be delivered in boxes, and each box contains 17 vials each with 100 mg hydrocortisone or placebo, and distilled water ampoules (2 ml) for dilution, thus, each box contains the whole study medication for one patient. Each Patient may receive study medication from one box only. Boxes and vials are labelled with the unique MedKit-ID.
The study medication is allocated to the patient by randomisation.
The study medication has to be stored at room temperature (≤ 25°C) in a safe place, direct exposure to heat or sun has to be avoided.
5.3 Drug Accountability

The study drug will be stored at BAG Healthcare GmbH until shipment to the centers by secure transportation.

The study medication will be delivered directly to the principal investigator or delegate of each site. The units have to be controlled for integrity and acceptance has to be acknowledged by fax to the KKSL. It is not wanted to open single boxes until the study drug is used. Each site has to provide a secure shipping address before delivery, and the investigators have to organize that the study drug is handed out only to authorized staff.

The eCRF will contain a sheet for drug accountability. The sheet includes following information: MedKit-ID, charge number, date and time of drug application, and dosage; the sheet is signed electronically by the responsible investigator.

Used vials should NOT be discarded but have to be collected and stored in the corresponding box. During the study period, the boxes for every patient should be kept at the bedside or other secure place to avoid confusion. After the study period, used boxes have to be stored in a secure place until information by the KKSL after the end of the whole trial that the study medication may be discarded at the site.
5.4 Administration of Study Drug

5.4.1 Application schedule

Each vial with the study medication contains a lyophilisate of 100 mg hydrocortisone or placebo which has to be diluted with 2 ml of distilled water under sterile conditions. The vials have to be controlled for complete solution of the lyophilisate.

The application scheme is:

- **A bolus** of 50 mg hydrocortisone or placebo is administered ONCE at the beginning of application of study medication as a loading dose.

For bolus application, the lyophilisate of one vial is diluted with 2 ml of distilled water. One ml of this dilution (= 50 mg hydrocortisone or placebo) is diluted to 10 ml with normal saline and administered intravenously. The bolus is immediately followed by **Continuous infusion** of the study drug:

- **Days 1-5**: Dilute 2 x 2 ml of study drug (2 vials = 200 mg hydrocortisone or placebo) in a 50 ml syringe with normal saline. Infusion rate: 200 mg/24 hours.
- **Days 6-7**: Dilute 1 x 2 ml of study drug (1 vial = 100 mg hydrocortisone or placebo) in a 50 ml syringe with normal saline. Infusion rate: 100 mg/24 hours.
- **Days 8-9**: Dilute 1 x 1 ml of study drug (1/2 vial = 50 mg hydrocortisone or placebo) in a 50 ml syringe with normal saline. Infusion rate: 50 mg/24 hours.
- **Days 10-11**: Dilute 1 x 1/2 ml of study drug (1/4 vial = 25 mg hydrocortisone or placebo) in a 50 ml syringe with normal saline. Infusion rate: 25 mg/24 hours.

The term ‘day’ in the context of study drug application refers to the 24 hour period of the administration of the study drug, which may be different from the period of the study day.

**NOTE:** In patients who develop septic shock, the study medication is discontinued, and commercially available hydrocortisone may be administered at the discretion of the investigator. In the case of discharge of the patient from the ICU before day 11 (last day of study medication), it is recommended to continue the application of the study medication if applicable to the infrastructure of the hospital. If the study medication is continued, investigators will ensure that application of the study medication is performed according to the protocol.

5.4.2 Compliance

In this study, compliance of the patient is not of concern, since all patients receive the study medication by infusion during their stay in the ICU or in the hospital, respectively.
5.4.3 Handling of Adverse Drug Reactions (ADR)

Prolonged administration of high doses of glucocorticoids may induce several side effects (see Summary of Product Characteristics [SmPC]). It is not anticipated that infusion of 200 mg hydrocortisone or less over several days induces severe adverse drug reactions. Hypersensitivity reactions to hydrocortisone have been reported but are extremely rare and are mostly due to additives. Patients are monitored for adverse events (see section 7).

In the case a severe adverse drug reaction is strongly suspected, the study medication has to be discontinued. In the case of hypersensitivity reactions, patients have to be treated according to standard procedures.

5.4.4 Contraindication/Forbidden Concomitant Medication

Application of the study medication is contraindicated in patients with known hypersensitivity to hydrocortison-21-hydrogensuccinate, natrium-monohydrogenphosphate, or mannitol (placebo). During the study period of 28 days, patients are not allowed to receive other glucocorticoids than the study medication for treatment of severe sepsis. In the case of an emergency situation (e.g. anaphylaxis, severe asthma) patients may receive any medication which is indicated, including glucocorticoids. There is no forbidden concomitant medication in addition to the study medication.

5.5 Blinding and Unblinding

The study medication is blinded to the investigators, ICU-staff, scientific coordinator, steering committee, and all other staff directly involved in patient care. The randomisation code for treatment is provided by KKSL to BAG Healthcare GmbH for preparation of labelling. Emergency envelopes are prepared and provided to the BAG by the KKSL. The blinding code is retained by the KKSL.

Each box of study medication has an emergency envelope, which contains the treatment assignment of the patient. Envelopes have to be stored in a secure place at the trial site. Emergency unblinding for adverse events may be performed by opening the emergency envelopes. **Unblinding may be done ONLY if the care given to the patient would be altered if the patient’s treatment assignment were known.** It is recommended that investigators consult the scientific coordinator or medical consultant (Jena) before unblinding. Unblinding has to be documented in the eCRF. Emergency envelops are recollected at the end of the study and controlled for intactness during and at the end of the study.

Deaths and serious adverse events will be reviewed by the scientific coordinator or the medical consultant (Jena) as the substitute, in a blinded manner. If a death or serious adverse event is unexpected and considered to be related to the drug (SUSAR) either by the investigator,
scientific coordinator, or medical consultant (Jena), a member of the KKSL pharmacovigilance team will unblind the single case to perform the SUSAR reporting (see section 7).
6  INDIVIDUAL TRIAL PROCEDURES

6.1  Screening of eligible patients

Examination of in- and exclusion criteria of potentially eligible patients is performed by the use of a predefined screening log. The reason for non-inclusion has to be documented. Every eligible patient has to be documented on the screening log.

As a part of checking in- and exclusion criteria, ongoing or recent (within the last 30 days) participation of a patient in an interventional clinical study has to be carefully examined. Participation in another interventional clinical study is an exclusion criterion.

In women with child bearing potential, a pregnancy test has to be performed before inclusion into the study. Only non-pregnant women can be included into the study. Effective contraception during the study is assumed by sexual abstinence due to the severity of the disease and hospitalisation.

6.2  Patient Information and Informed Consent

Written informed consent will be obtained before inclusion of a patient into the study. The original of the signed informed consent remains in the investigator site file, a copy is provided to the patient (or surrogate, if a patient is not able to give informed consent by oneself, see below) together with the patient information sheet.

The investigator must explain to each trial subject (or surrogate) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail to each trial subject. Each trial subject (or surrogate) must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician.

The informed consent will be given by means of a standard written statement, written in non-technical language. The trial subject (or surrogate) should read the statement and consider his/her decision before signing and dating the document, and should be given a copy of the signed document. If written consent is not possible, oral consent by the patient can be obtained if witnessed by a signed statement from one or more persons not involved in the study, mentioning why the patient was unable to sign the form. Apart from the exemptions below, no patient can enter the study before his/her informed consent has been obtained.
6.2.1 Informed consent in patients not able to give informed consent by themselves

It is recognised that due to the severity of disease (severe sepsis) most patients may not be able to give informed consent by themselves. In the case that informed consent can not be obtained from the trial subject, informed consent must be obtained from a legal representative or proxy (‘Bevollmächtigter’).

Trial sites may consider established procedures accepted by local ethics committees for gaining informed consent in critically ill patients who are not able to give informed consent by themselves:

- Patients may be enrolled in the study if the relative is asked immediately, probably by telephone call, for the suspected intention of the patient. The suspected intention of the patient has to be documented. The competent court is informed immediately about the suspected intention of the patient and has to appoint a legal representative immediately. If the relative refuses participation of the patient in the study, the patient may not be enrolled.

- It is assumed that the effect of ldHC is most effective to prevent shock when therapy is initiated as early as possible after development of severe sepsis. It is possible, that informed consent by a legal representative or proxy can not be obtained in due time. Since application of low dose hydrocortisone is an add-on therapy, and patients included into the study may profit from shock prevention, preliminary inclusion in the study is possible, if an independent medical consultant certifies that the patient is unable to give informed consent and that the patient may profit from inclusion in the study. The independent consultant has not to be affiliated to the institution or staff performing the study or to the staff taking routine medical care of the patient, and has to provide written rationale for giving informed consent. In addition, informed consent by the legal representative or proxy has to be obtained as early as possible.

- Other established procedures, if applicable.

If the patient has not appointed a proxy in advance, appointment of a legal representative by the court has to be initiated immediately. If the legal representative or proxy refuses participation in the study retrospectively, the patient has to be excluded from the study immediately. In this case, all further data acquisition is stopped and blood samples are destroyed. Data which have been obtained until this time may be used if criteria 6.2.3 are met.

Patients who are unable to provide informed consent by themselves have to be informed about the study as early as possible with regard to the medical condition, and informed consent has to be obtained retrospectively. If a patient was unable to give primary informed consent and refuses consent retrospectively, all data have to be deleted unless criteria in 6.2.3 are met. In any case, blood samples have to be destroyed.
6.2.2 Informed consent for DNA-sample

A DNA-sample will be obtained once during the study. Scientific evaluation of the DNA will be performed only in the context of the underlying disease (sever sepsis). The DNA-sample will be used to identify single nucleotide polymorphisms and/or for the evaluation of candidate genes to identify genetic factors which may be important in the pathophysiology of sepsis and for the development of new therapeutic concepts.

Independent from participation in the study, the patient may withdraw consent for using the DNA-sample. Sampling of the DNA is not time critical. DNA will only be obtained if written informed consent is given by the patient, proxy, or legal representative.

An independent trustee will be informed about collection of the DNA-sample. The trustee receives the name of the patient, the pseudonym of the patient (patient-ID), and the identification number of the DNA-sample. At any time (also after the end of the study), the patient may refuse the use of the DNA by information of the trustee. Only the trustee has the information to link the DNA-sample to the individual patient. The trustee informs the central blood storage bank to destroy the DNA-sample and all data, which has to be confirmed by the central probe bank to the trustee.

6.2.3 Withdrawal of informed consent

The patient (or proxy, legal representative) may withdraw the consent to participate at any time of the trial without giving the reason for it. Nevertheless, the patient should be asked for the reason of the premature termination but he/she should also be aware, that he/she needs not to answer this question. The patient must be informed that choosing not to participate or to withdraw the consent will not affect his/her subsequent medical treatment or relationship to the treating physician.

Date of enrolment and date of and reason for withdrawal are to be documented in any case. The patient is to be informed that in case of revocation of his/her consent; the stored data may be used further, as may be necessary:

- to assess effects of the study drug to be tested
- to guarantee that the interests of the patient are not impaired
- to comply with the regulatory requirements.

6.3 Enrolment and Randomisation

6.3.1 Randomisation

Before randomisation of the patient into the study, the investigator has to verify that the patient meets all inclusion and no exclusion criteria. Randomisation is performed via an internet-based automatic system which is provided by the KKSL. The automatic system informs the KKSL
automatically about randomisation of a patient. If randomisation is not possible via internet (e.g. system error) a study medication box is randomly chosen by the investigator. The investigator then has to inform the KKSL about the MedKit-ID depicted on the study medication label.

It is recognized that sepsis is a dynamic process, thus, it may be the case that patients who have been randomised develop septic shock before the first study drug can be administered. Patients, who have been randomised, but develop septic shock before the study medication can be administered, may not receive the study medication, because the primary endpoint of the study had been reached. In this special case, the KKSL will be informed by the investigator that no study medication had been administered, and only a minimal set of data will be obtained. The patient will be registered as randomised but excluded from the study due to development of septic shock before administration of study medication. Only patients who have received any study drug are analyzed on an intention-to-treat basis, irrespective of the time septic shock develops.

6.3.2 Violation of eligibility criteria
In general, the violation of eligibility criteria is not a reason for premature withdrawal of the patient from the study.

If after randomisation it is noticed that the patient was not eligible at the time of randomisation, this has to be reported to the scientific coordinator as soon as possible. The scientific coordinator will discuss with the investigator if further treatment within the HYPRESS-study is indicated. Documentation of patient clinical data will be continued.

6.3.3 Handling of the DNA-sample
The DNA-sample may only be obtained if informed consent has been gained from the patient, proxy, or legal representative.

For the DNA-sample, two provided blanks are to be completed. One blank, which contains the bar-code, remains with the DNA-sample, and the barcode is attached to the probe. No additional labelling of the probe is allowed! The DNA-sample and the corresponding blank are send to the central SepNet blood sample storage bank.

The other blank contains information for the trustee and has to be faxed to the number:

Fax-No.: 03641 876 779.

The trustee will send a confirmation of receipt to the investigator. After the confirmation has been received, the original blank sent to the trustee by the investigator has to be destroyed. This ensures that only the trustee is able to identify a patient to the corresponding DNA-sample.
6.4 Treatment of Trial Subjects

General recommendations

No special treatment algorithms are included in the HYPRESS protocol as study-specific procedures for treatment of patients with severe sepsis. However, for participation in HYPRESS, it is a pre-requisite that patients are treated according to the S2-guidelines for treatment of patients with severe sepsis as published by the German Sepsis Society [REINHART 2006]. It is critical for conducting HYPRESS that measures taken within the first 6 hours after onset of severe sepsis recognize recommendations for Early Goal Directed Therapy (EGDT) (see below). Irrespective of the inclusion time (within the first six hours after diagnosis of severe sepsis or later) measures for EGDT will be documented in the eCRF.

Among other recommendations, the following is regarded as recommended intensive care treatment for patients with severe sepsis:

- Adequate source control of infection (e.g. surgery).
- Blood cultures prior to antibiotic treatment (see below).
- Early empiric antibiotic treatment (within 1 hour after diagnosis of severe sepsis).
- ScvO₂-guided volume therapy within the first 6 hours after diagnosis of severe sepsis.
- The use of norepinephrine and dobutamine as catecholamines of first choice. Epinephrine, dopamine, or vasopressin should not be used in the first line. Low-dose dopamine is not to be used.
- Crystalloids should be regarded as volume of first choice. HES (200/0.5) was associated with an increased risk of renal failure in the SepNet VISEP study. The use of HES 200/0.5 is discouraged in patients with severe sepsis. Although there are no data for other HES preparations with respect to renal failure in severe sepsis, the use of alternative HES preparations is not recommended. If HES is used, the daily dose as recommended by the manufacturer should not be exceeded.
- Lung-protective mechanical ventilation (plateau pressure < 30 mbar) in the case of ARDS/ALI.
- Early enteral nutrition.
- Maintenance of blood glucose < 150 mg/dl.
- Application of activated Protein C when indicated.
- Early Goal Directed Therapy (see below).

It is necessary for conducting HYPRESS that patients are monitored by a central venous catheter and arterial line at least during the first 5 days of the study. Both are considered as
standard procedures in patients with severe sepsis. The use of a pulmonary artery catheter (PAC) may be indicated in individual patients (e.g. pulmonary hypertension), however, for conducting HYPRESS, the use of a PAC is not obligatory.

**Antibiotic therapy**

Intravenous antibiotic therapy should be started as early as possible and within the first hour of recognition of severe sepsis. Appropriate cultures should be obtained before initiating antibiotic therapy, but should not prevent prompt administration of antimicrobial therapy. Initial empirical anti-infective therapy includes one or more drugs that have activity against all likely pathogens (bacterial and/or fungal) and that penetrate into the presumed source of sepsis. Patients with severe sepsis warrant broad-spectrum therapy until the causative organism and its antibiotic susceptibilities are defined. The antimicrobial regimen should be reassessed daily to optimize activity, to prevent the development of resistance, to reduce toxicity, and to reduce costs.

**Source control**

An anatomic diagnosis of the site of infection eliciting severe sepsis and source control measures should be established as soon as possible. Source control include e.g. the drainage of an abscess or local focus of infection, the debridement of infected necrotic tissue, the removal of a potentially infected device, or the definitive control of a source of ongoing microbial contamination. When intravascular access devices are a possible source of severe sepsis, they should be promptly removed after establishing other vascular access.

**Blood cultures**

Two to three blood cultures should be obtained, each consisting of a pair of aerob and anaerob bottles. It is not necessary to follow a defined time frame in intensive care patients. Blood cultures should be obtained before antibiotic treatment, in patients already receiving antibiotics, blood cultures should be obtained before application of the next antibiotic dosage.

**Septic shock**

Patients who develop septic shock during the study may receive _ldHC_, and the study medication has to be discontinued in that case. The indication for application of _ldHC_ is made by the physician in charge or investigator, and should recognize recommendations for the use of _ldHC_ in patients with septic shock. For this, updated recommendations of the Surviving Sepsis Campaign 2007 will be provided to investigators. The preliminary recommendation indicates the use of _ldHC_ in patients who are poorly responsive to fluid resuscitation and vasopressor therapy.
Early goal directed therapy (EGDT) and HYPRESS:
EGDT is not part of the HYPRESS protocol, since EGDT has to be initiated immediately after
diagnosis of severe sepsis, and patients may be included within 48 hours after diagnosis of
severe sepsis; however, it is strongly recommended to include patients as early as possible. For
conducting the trial, adequate initial treatment of patients with severe sepsis is essential. It is
critical that in the first hours of severe sepsis, patients may require large amounts of volume.

For an adequate volume loading, patients with suspected hypovolemia should be immediately
treated with at least 500-1000 ml crystalloids or 300-500 ml colloids (see restriction of the use of
HES above) over 30 min. Continued volume therapy may be indicated based on the individual
response to fluids (arterial pressure, central venous pressure, central venous oxygen saturation,
and diuresis) and tolerance to fluids (hypervolemia). It is recognized that patients may need
several liters of fluids within the first hours of severe sepsis, and that vasopressors may be
indicated in severe hypotension to bridge the time until adequate volume loading is achieved.
In HYPRESS, only norepinephrine should be used as the vasopressor of first choice.
Epinephrine, vasopressin, and dopamine should not be used routinely, and should not be used
as vasopressors of first choice. The use of low-dose dopamine for ‘renal protection’ is not
indicated and can not be recommended in critically ill patients due to ineffectiveness and side
effects.

By definition, patients are in septic shock when they need vasopressors. If after EGDT, patients
remain hemodynamic stable (MAP ≥ 65 mmHg or SAP ≥ 90 mmHg) for at least 2 hours without
vasopressors, these patients are defined to be not in shock, i.e. these patients are eligible for
HYPRESS. Hemodynamic variables will be monitored at within the first 24 hours after
enrollment and during the first 6 hours after diagnosis of severe sepsis (depending on the time
of inclusion these observational periods may overlap!).

For initial resuscitation of patients with severe sepsis, it is recommended to achieve the
following hemodynamic goals:

- Central venous oxygen saturation (ScvO₂) ≥ 70 %.
- Central venous pressure (CVP) ≥ 8 mmHg in non-ventilated patients (≥ 12 mmHg in
  ventilated patients).
- Mean arterial pressure ≥ 65 mmHg or systolic arterial pressure ≥ 90 mmHg.
Although effectiveness of EGDT has been demonstrated only for patients with initially high lactate values, it is recommended to maintain the goals after initial resuscitation by regularly reassessment. To achieve a ScvO₂ ≥ 70 %, therapy with volume, red blood cells, and dobutamine may be indicated. If a pulmonary artery catheter is used, a mixed venous oxygen saturation ≥ 65 % may be regarded as equivalent to a ScvO₂ ≥ 70 %.

**Procedures in HYPRESS**

The HYPRESS study consists of three periods (see also schedule of assessment and procedures):

The **pretreatment period** spans the time between ICU admission and time of application of the study medication.

The **treatment period** (STUDY DAY 1-14) spans the time from first application of the study medication until day 14, i.e. the treatment period consists of the time period the study medication is administered plus three days of observation.

The **posttreatment period** (FOLLOW UP) spans the time from day 15 until hospital discharge (FU HD) and 6 months (FU 180), and 6 months after hospital discharge for PTSD and HrQoL.

**Pretreatment period:**

**Pre-inclusion:**
- Screening of eligible patients
- Documentation of eligible patients in the screening log

**Inclusion:**
- Assessment of in-/exclusion criteria
- Informed consent
- Informed consent for DNA-sample (at any time possible)
- Randomisation

**Baseline (Day 0):**
- Verification of in-/exclusion criteria
- Documentation of concomitant and recent history of medication, medical history, antibiotic treatment, demographic data, fluid intake, insulin requirement, diuresis, hemodynamic and ventilation variables.
- Documentation of variables and treatment after diagnosis of severe sepsis (within first 6 hours)
- Documentation of data for SOFA, CAM-ICU, RASS (data obtained within 24 h before application of study medication).
- Documentation of data for SAPS 2, SAPS 3, APACHE II score (data obtained within 24 h before application of study medication)
- Documentation of data for GCS score.
- Documentation of MRC scale.
- Documentation of routine laboratory data.
- Collection of study specific blood samples (see schedule for assessment and procedures).
- ACTH-test (in selected sites) (see section 12)

**Treatment period (Study day1-14):**

- Application of study medication until day 11 (see 5.4).

Daily procedures:

- Assessment of septic shock.
- Assessment of organ dysfunction (SOFA score), GCS, RASS, and CAM-ICU score.
- Documentation of chart data (lab values, hemodynamic and ventilation parameters, fluid intake, concomitant medication, antibiotics etc.).
- Record days of mechanical ventilation and renal replacement.
- Assessment of safety issues (secondary infections, hyperglycemia, hypernatremia, GI-bleeding, weaning failure, muscle weakness).
- Assessment of adverse events

**Posttreatment period (Follow-up):**

Note: If the patient is discharged from hospital before day 28, assessments are performed on hospital discharge, except 28-day survival status.

**Day 28**

- Survival status (NOTE: if the patients is discharged from the hospital before day 28, information about the survival status should be obtained by contact with the patient, legal representative, proxy, or other hospital)
- Assessment of adverse events
- Assessment of septic shock
- Assessment of weaning failure
• Assessment of muscle weakness
• Assessment of secondary infections
• Assessment of renal replacement therapy
• Assessment of days of mechanical ventilation
• Assessment of delirium (CAM-ICU)

ICU-discharge
• Survival status
• Assessment of weaning failure
• Assessment of muscle weakness
• Assessment of renal replacement therapy
• Assessment of days of mechanical ventilation
• Assessment of delirium (CAM-ICU)

Hospital discharge
• Survival status
• PTSD and HrQoL questionnaires
• Informed consent for sending personal data to the Charité study team for second PTSD and HrQoL questionnaires.

180-day
• Survival status

180-day after Hospital discharge
• PTSD and HrQoL

6.5 Premature Termination of Therapy or Follow-up

Each premature termination of the trial therapy as well as every premature termination of follow-up has to be documented by the responsible investigator. If possible, date, circumstances of and reason for the termination should be documented in detail, and communicated to the KKSL / Data Management.

6.5.1 Premature termination of trial therapy of an individual patient

Septic shock:
The administration of the study medication has to be terminated, if the patient develops a vasopressor dependent septic shock despite adequate fluid loading (for a detailed definition of septic shock see appendix). The patient may then receive commercially available
hydrocortisone at the discretion of the investigator. The patient remains in the study also after cessation of study drug application, and that documentation has to be continued.

**Protocol violation:**
In the case of protocol violation (e.g. the patient receives glucocorticoids accidentally), the study drug application should be continued. Date, circumstances of and reason for the protocol violation should be documented in detail and communicated to the KKSL.

**Transfer to another hospital:**
In the case, the patient is transferred to another hospital or institution the study medication has to be discontinued, and documentation is stopped. If the patient is transferred to another hospital or institution before day 14 without shock, the investigator should receive information about shock development until day 14 and survival status at day 28 from the other hospital or institution.

**Transfer inside the hospital:**
In the case, the patient is transferred inside the hospital (e.g. to an intermediate care unite), it is at discretion of the investigator to decide, if the study can be continued. If the study medication is continued, the investigator has to take care that the study medication is administered according to the protocol. The documentation has to be continued, if applicable.

**Serious adverse events see 7 ff.**

**General remark:**
Premature termination of study drug application for other reasons than septic shock has to be documented in detail and communicated to the KKSL. In general, premature termination should be avoided. In case of a premature termination of the trial drug administration, reasons/circumstances and if applicable the final status have to be documented. If the patient does not withdraw the consent for further follow-up, he or she should be followed-up as planned.

**6.5.2 Premature termination of follow-up of an individual patient**
In case the patient misses the scheduled visits (e.g. second PTSD questionnaire), the scientific coordinator or associated personal staff will contact the site investigator who will contact the patient to motivate him/her for further follow-up. Follow-up for PTSD is only possible if the patient gives written informed consent at hospital discharge.

**6.5.3 Plan of further treatment**
There is no necessity for further treatment plan for patients enrolled in HYPRESS, since patients may receive all standard treatment including the trial drug, which is an approved commercially available drug (hydrocortisone).
7 ADVERSE EVENTS (AE/SAE)

7.1 Adverse Event (AE)

7.1.1 Definition
An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical or medical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a medicinal (investigational) or medical product, whether or not it is considered to be related to the medicinal (investigational) product (ICH-Guideline E2A).

Adverse events encompass illness, signs of illness (including pathological laboratory findings) and symptoms that initiate during the trial or previous conditions that become worse.

According to ICH-Guideline E2A, the term adverse drug reaction (ADR) means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

7.1.2 Documentation and Reporting
Severe sepsis and septic shock rank among the most life threatening diseases. In the SepNet prevalence study the ICU-mortality was about 47 %. About 95 % of patients are mechanically ventilated and analgosedated. About 70 % of patients develop acute renal failure or septic shock. Parameters of organ dysfunction and metabolism are almost always affected depending of the severity of sepsis.

Therefore, the death of a patient and other sepsis-related events are recorded as clinical events in the CRF. The documentation of these events is part of the daily assessment of the severity of organ dysfunction (e.g. SOFA-Score). These data will be recognized in the safety and efficacy analysis. The following sepsis-related clinical events have only to be recorded as adverse events (AE), if the investigator deems the event possibly related to the study medication:

- Death due to severe sepsis / septic shock.
- Development of septic shock.
- SIRS-related criteria and vital parameters (tachycardia, bradycardia, hyperthermia, hypothermia, leukocytosis, leukopenia, tachypnoe, dyspnoea).
• Hepatic dysfunction (increase of liver enzymes or bilirubin above normal, or an increase compared to baseline).
• Renal dysfunction (acute renal failure, renal insufficiency, renal replacement therapy, rises of urea or creatinine compared to baseline).
• Septic encephalopathy (somnolence, delirium etc.).
• Coagulation dysfunction (disseminated intravascular coagulation, thrombocytopenia, thrombocytosis, coagulopathy).
• Respiratory dysfunction (acute respiratory failure, acute lung injury, mechanical ventilation, hypoxia, a decrease of PaO₂/FiO₂ ratio).
• Metabolic and microcirculatory dysfunction (metabolic and respiratory acid-base changes, hyperkalemia, hypokalemia, increase of lactate, capillary leakage, acrocyanosis, etc).

Blood glucose and sodium values are closely monitored in the CRF. Hyperglycemia (blood glucose > 150 mg/dl) and hypernatremia (sodium > 155 mmol/l for more than 24 hours) have only to be recorded and reported as an AE until day 14, if the investigator deems the event to be related to the study drug application AND if the event meets the criteria of a SAE (see below).

Emergency surgical procedures have only to be recorded as AE, if the investigator deems the event to be related to the study medication.

Possible side effects of hydrocortisone may be also symptoms and the consequences of severe sepsis and septic shock. The following events have to be recorded as AEs until day 28, irrespective of the causal relationship to the study drug:

• **Muscle weakness**
  Muscle weakness is defined as clinical signs of muscle weakness which are not due to pre-existing neurological or muscular disease. Muscle weakness is clinically assessed by the MRC scale (see appendix), a score < 48 indicates clinically relevant muscle weakness.

• **Weaning failure**
  Weaning failure is defined as re-intubation within 24 hours after extubation OR the need of continuous non-invasive mechanical ventilation with pressure support for more than 48 hours after extubation. Re-intubation for diagnostic (e.g. bronchoscopy) or planned
surgical procedures (e.g. wound debridement, peritoneal lavages, osteosynthesis, tracheotomy etc.) should not be reported as an adverse event.

- **Secondary infection**
  Secondary infection is defined as a microbiologically proven new infection which occurs more than 48 hours after application of first study medication, with or without adaptation of the antibiotic regime, OR clinical evidence of a new source of infection with or without microbiological verification (e.g. secondary hospital acquired pneumonia). Colonisations unless proven to be invasive (e.g. candida species) or colonisations with typically non-pathogenic micro-organisms are not considered as secondary infection.

- **Gastrointestinal bleeding**
  GI-bleeding is defined as an acute bleeding which requires treatment with more than 1 unit of red blood cells within 24 hours.

**Other events** not considered to be typically associated with severe sepsis/septic shock, and which are therefore unexpected adverse events, have to be recorded as AE. (e.g. stroke, myocardial infarction, pulmonary embolism).

It is the responsibility of the investigator to document all adverse events in the eCRF. Documentation of adverse events includes the kind of event, the beginning and end of the event, the seriousness of the event, causality to study medication, and which actions have been taken with regard to the event. Adverse events occurring until day 28 have to be reported.

### 7.2 Concomitant Diseases

Due to the high morbidity and mortality of patients with severe sepsis, variances of concomitant diseases will not be regarded as adverse events in this study.

### 7.3 Serious Adverse Event (SAE)

#### 7.3.1 Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect (not applicable in HYPRESS)
The following events are reported as SAE:

- As defined in 7.1.2, all expected events (clinical events and possible side effects), as long as they are documented as AE (i.e. the investigator suspects a causal relationship to the study drug application), and when the criteria of SAE definition (see above) are fulfilled.

- As defined in 7.1.2, events which have to be reported as AE irrespective of a causal relationship to the application of the study drug, and when the criteria of SAE definition (see above) are fulfilled.

- All events which are not defined in 7.1.2, and thus are unexpected adverse events, when the criteria of SAE definition (see above) are fulfilled.

**NOTE:**
The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (see ICH guideline E2A, section IIIB)

### 7.3.2 Documentation and reporting

Serious adverse events are documented by the investigator on SAE-CRF pages and have to be transmitted by FAX within 24 hours after recognition of the event to the scientific coordinator (representative of the sponsor for scientific issues). The SAE may be forwarded to the SepNet medical consultant in Jena as the substitute.

The scientific coordinator/medical consultant (Jena) verifies whether the reported SAE fulfills the SAE-criteria as defined in 7.3.1. If the reported SAE does not meet the criteria as defined 7.3.1, no further action will be taken, and the reported SAE will be filed with a note at the study coordination center of the scientific coordinator/medical consultant (Jena). If the reported SAE meets the SAE-criteria as defined in 7.1.3, the scientific coordinator/medical consultant (Jena) verifies completeness and plausibility of the SAE reported by the investigator. In addition, the scientific coordinator/medical consultant (Jena) reviews causality and expectedness of the SAE. The second evaluation of the SAE and the SAE-CRF provided by the investigator has to be send to the KKSL pharmacovigilance team within two days per FAX (0341-9716278). If
additional information of the SAE becomes evident at a later time, all information has to be provided to the scientific coordinator/medical consultant (Jena) immediately after recognition by the investigator. The information is then forwarded to the KKSL.

All SAEs will be documented electronically at the KKSL in a SAFETY-database (eResearch Technology). This documentation includes all data provided by the SAE-CRF, follow-ups, and the second evaluation of the medical consultant. The data of diagnosis and reaction will be coded by MedDRA.

In case of the death of a patient the investigator has to forward to the leading ethics committee, in multi-centre trials to all involved ethics committees, as well as to the competent regulatory authorities (BfArM) and to the scientific coordinator/medical consultant (Jena) all additional information required on request.

The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects (pseudonym) and may not contain the subjects' names and/or addresses. The patient identification list which contains the patient code number and personal data has to be stored in the investigator site file to ensure the link to the patient personal data at any time.

The sponsor/scientific coordinator provide a safety report once a year or on request according to the ‘detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’. The safety-report includes a detailed risk-benefit analysis, a list of all serious adverse reactions (SARs), and a summary table. The safety report will be transmitted to the leading ethics committee and BfArM. The KKSL supports the sponsor/scientific coordinator in preparing the safety-report.

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<thead>
<tr>
<th>Scientific Coordinator</th>
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<tr>
<td>Charité Universitätsmedizin Berlin</td>
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<tr>
<td>Universitätsklinik für Anästhesiologie mit Schwerpunkt operative Intensivmedizin CCM/CVK</td>
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<td>Campus Virchow-Klinikum</td>
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<td>Phone: 030 450 651048 or</td>
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<td>FSU-Jena</td>
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<td>Klinik für Anästhesiologie und Intensivtherapie</td>
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7.4 Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)

7.4.1 Definition
Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product are contained in the SmPC (Summary of Medicinal Product Characteristics) should be used to verify if the adverse reaction has been previously described.

7.4.2 Documentation and reporting
The KKSL which is mandated by the sponsor for pharmacovigilance issues submits all information available about a SUSAR immediately, latest within 15 days after the event becomes known, to the leading ethics committee, the competent regulatory authority (BfArM), and to all principal investigators.

If a death or serious adverse event is unexpected and considered to be related to the drug (SUSAR) either by the investigator, scientific coordinator, or medical consultant (Jena), a member of the KKSL pharmacovigilance team will unblind the single case to perform the SUSAR reporting.

In the case of death or life-threatening event caused by a SUSAR the leading ethics committee, the competent regulatory authority (BfArM), and all principal investigators must be informed by the KKSL within 7 days after the event becomes known. Additional information has to be provided within further 8 days. The information about a SUSAR is only transmitted to the principal investigator of each site; the principal investigator is responsible for transmitting the information to the investigators.

The KKSL provides information about SUSARs and relevant SARs on CIOMS I forms as recommended by the ‘4. Bekanntmachung zur Anzeige von Nebenwirkungen und Arzneimittelmissbrauch nach §63b Abs. 1 bis 8 des Arzneimittelgesetzes (AMG), 2005’. The CIOMS I form will be electronically prepared by the software tool and stored in the database. The time of sending the CIOMS I form to regulative authorities and principal investigators will be documented in the database.

7.5 Therapeutic Procedures
AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.
The action taken by the Investigator must be documented:

a) In general:
   - None
   - Drug therapy started
   - Test performed (e.g. laboratory)
   - Unknown
   - Not applicable

b) On the investigational product:
   - Treatment stopped
   - Dose reduced
   - Dose increased
   - Dose not changed
   - Unknown
   - Not applicable

7.6 Classification of the Adverse Event

7.6.1 Severity
Assessment of severity according to CTCAE V3.0
   - Mild (= awareness of symptoms but does not interfere with routine activities)
   - Moderate (= discomfort enough to interfere with routine activities)
   - Severe (= impossible to perform routine activities)
   - Life-threatening or resulting in disability/incapacity
   - Death caused by AE

7.6.2 Causal relationship
The investigator must judge whether or not, in his opinion, the Adverse Event was connected with the administration of the investigational product according to the classification given below (Venulet and Ham, 1996). Each Adverse Event has to be reported, even if the investigator feels that it is not connected with the administration of study drug (exemptions are defined in 7.1.2).
   - Possible
   - Not possible

The relationship is possible, if one of the following criteria according to WHO-UMC is fulfilled:
- Plausible timing, and can not be explained by concomitant diseases or other products, and, and known pharmacological or phenomenological reaction and positive re-application of the product, if necessary
- Plausible timing, and unlikely connection to concomitant diseases or other products, and positive reaction upon withdrawal
- Plausible timing, but could be explained by concomitant diseases or other products, information on withdrawal is incomplete or unclear.
- For a complete evaluation, further information is necessary.
- Evaluation is impossible due to inadequate or contradictory information.

The **relationship is not possible**, if the following criterion according to WHO-UMC is fulfilled:
- The timing renders a causal relationship unlikely and concomitant disease or other products can serve as a plausible explanation.

### 7.6.3 Expected/Unexpected

An Unexpected AE is an AE, the nature or severity of which is not consistent with the applicable product information (SmPC).

The separation expected/unexpected must be decided from the perspective of previously described untoward reactions, not on the basis of what might be anticipated from pharmacological properties of a medicinal product.

### 7.6.4 Outcome

The outcome of an AE has to be classified as follows:
- recovered/resolved
- recovered/resolved with sequelae
- not recovered/not resolved
- fatal
- unknown

**NOTE**: A subject's death per se is not an event, but an outcome. The event which resulted into subject's death must be fully documented and reported, even in case the death occurs within four weeks after test drug treatment end, and without respect of being considered treatment-related or not.
8 BIOMETRICAL ASPECTS

8.1 Randomisation Algorithm

Randomisation is performed using a modification of Pocock’s algorithm. This method ensures that treatment group numbers are evenly balanced over the whole recruitment period. The allocation ratio between the two arms of the study is 1:1. Randomisation will be stratified by the participating center and gender.

8.2 Endpoints

8.2.1 Primary endpoint

Primary endpoint of the study is the proportion of patients with septic shock (i.e. the number of patients with septic shock divided by the total number of patients) within 14 days in the control arm ($\pi_C$) compared with the treatment arm ($\pi_T$).

8.2.2 Secondary endpoints

- 28-day mortality (proportion of patients who die within 28 days from any cause)
- 90 and 180-day mortality
- ICU-mortality
- Hospital mortality
- Time to death from any cause and sepsis-related death
- Length of ICU stay
- Length of hospital stay
- Time to septic shock and/or death within 14 days
- Frequency and duration of mechanical ventilation until ICU discharge
- Frequency and duration of renal replacement until ICU discharge
- Mean total SOFA (organ dysfunction) and mean SOFA sub-scores until ICU discharge but day 14 at maximum

8.2.3 Safety endpoints

- Frequency of weaning failure within 28 days
- Frequency and severity of muscle weakness until ICU discharge
- Frequency of GI-bleeding within 28 days
- Frequency of secondary infections within 28 days
- Blood sodium level and frequency of hypernatremia (> 155 mmol/l) within 14 days
- Blood glucose level and frequency of hyperglycemia (> 150 mg/dl) within 14 days
8.3 Statistical Hypotheses

The aim of the study is to demonstrate that IdHC can reduce the rate of septic shock in patients with severe sepsis. However, the alternative hypothesis will be formulated to show also the possible inferiority of the treatment arm (two-sided design). Thus, the null hypothesis and the alternative hypothesis are as follows:

\[ H_0: \pi_C = \pi_T \]

\[ H_1: \pi_C \neq \pi_T \]

The experiment-wise type-I error rate will be set to \( \alpha = 0.05 \). A power of \( (1-\beta) = 0.8 \) will be aimed at.

8.4 Statistical Methods

8.4.1 Planned methods for analysis

The primary endpoint will be analyzed using the Chi-Square test. The analysis will be conducted according to the “intention-to-treat” principle.

Secondary endpoints are evaluated by means of parametrical or non-parametrical tests, depending on the given scale level and type of distribution of the observed variables. In case of small random samples, lack of balance, sparse data sets (in contingency tables), and data sets containing ties, exact inferential methods will be used.

Evaluation of time to event data is initiated by graphical presentation using Kaplan-Meier curves and statistical comparison using the Log-Rank test. Apart from such comparison, exploratory evaluation may include investigation of covariates and their impact on the time until the onset of an event, using Cox regression. Such analyses are conducted to identify prognostic factors.

Logistic regression analysis will be used to determine the relationship between selected (suspected) explanatory variables and binary outcome variables. Where appropriate, estimates of effect sizes and the according confidence intervals will be calculated.

8.4.2 Analysis population

The intention-to-treat (ITT) population is defined by
- all patients randomised who have received at least once the study medication and
- who did not refuse participation in the study retrospectively (by themselves or a proxy or a legal representative) in case of study inclusion by relative or independent medical consultant.
The per-protocol (PPS) set is defined by all patients belonging to the ITT without severe violations of the study protocol. Before closure of the database and before unblinding it will be decided whether a patient is assigned to the PPS.

The Safety population is defined by all patients randomised who received at least once the study medication. In the safety analyses, patients will be evaluated according to the treatment they actually received, irrespective of the randomisation.

The interim, safety and the final analyses will be planned in detail in a Statistical Analysis Plan.

8.5 Interim Analysis

Two interim analyses will be conducted when the sample size has reached 1/3 and 2/3 of the target sample size. At each interim analysis, a formal analysis of the primary endpoint will be performed for the ITT population. Stopping boundaries are calculated in a group sequential design based on the alpha spending method (DeMets and Lan, 1994; Lan and DeMets, 1983; Hwang and Shih, 1990) as specified by O'Brien and Fleming (O'Brien and Fleming, 1979).

The rates for type-I and type-II errors at each stage are given in the following table (based on a two-sided test of proportions with continuity correction):

<table>
<thead>
<tr>
<th>Look</th>
<th>Relative Sample Size</th>
<th>Lower Boundary</th>
<th>Upper Boundary</th>
<th>Nominal Alpha</th>
<th>Incremental Alpha</th>
<th>Total Alpha</th>
<th>Incremental Power</th>
<th>Total Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interim 1</td>
<td>1/3</td>
<td>-3.71030</td>
<td>3.71030</td>
<td>0.000207</td>
<td>0.000207</td>
<td>0.000207</td>
<td>0.018887</td>
<td>0.018887</td>
</tr>
<tr>
<td>Interim 2</td>
<td>2/3</td>
<td>-2.51142</td>
<td>2.51142</td>
<td>0.012025</td>
<td>0.011890</td>
<td>0.012097</td>
<td>0.401411</td>
<td>0.420297</td>
</tr>
<tr>
<td>Final</td>
<td>1</td>
<td>-1.99302</td>
<td>1.99302</td>
<td>0.046259</td>
<td>0.037903</td>
<td>0.050000</td>
<td>0.382184</td>
<td>0.802482</td>
</tr>
</tbody>
</table>

The interim analyses will be performed by the KKSL. Together with each interim analysis, a safety analysis will be performed. The results of the interim and safety analyses (including a report about SAEs and SUSARs) will be reported to the DSMB, which will give a recommendation for either continuation or termination of the trial. The final decision on continuation or termination will be made by the sponsor in agreement with the steering committee of the study.

8.6 Final Analysis

The final analysis will be carried out in the ITT population after the target sample size of 380 randomised patients has been reached. A patient is informative with respect to the primary endpoint analysis if it is known whether or not the patient has experienced septic shock within 14 days.
8.7 Estimation of Effect Size

Data on the expected proportion of patients with septic shock in the control is available from several publications and from own data (see the following table).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of patients with severe sepsis who developed septic shock (shock / severe sepsis)</th>
<th>Percent</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone 1987</td>
<td>45 / 122</td>
<td>37%</td>
<td>mixed population</td>
</tr>
<tr>
<td>Rangel-Frausto 1995</td>
<td>78 / 196</td>
<td>40%</td>
<td>mixed population</td>
</tr>
<tr>
<td>Confalonieri 2005</td>
<td>10 / 23</td>
<td>43%</td>
<td>CAP</td>
</tr>
<tr>
<td>Vincent 2003</td>
<td>55 / 104</td>
<td>58%</td>
<td>mixed population</td>
</tr>
<tr>
<td>Katja 2001</td>
<td>14 / 58</td>
<td>24%</td>
<td>Peritonitis</td>
</tr>
<tr>
<td>von Dossow 2005</td>
<td>29 / 76</td>
<td>38%</td>
<td>HAP</td>
</tr>
<tr>
<td>SepNet (pers. comm)</td>
<td>55 / 159</td>
<td>35%</td>
<td>mixed population</td>
</tr>
</tbody>
</table>

According to these data, a proportion of $\pi_c = 0.4$ is assumed for the control group of the present study. It is expected that this proportion can be reduced in the treatment group to $\pi_t = 0.25$ (i.e. an absolute difference of 0.15, or a relative risk of 0.625, or an odds ratio of 0.5).

8.8 Drop-outs

A drop-out rate of 10% is expected. It will be assumed that drop-outs occur independently, and not related to any study arm.

8.9 Sample Size Discussion

8.9.1 Sample Size Calculation

The sample size was calculated using PASS 2002, Kaysville, Utah, USA. Sample sizes of 169 per group achieve 80% power to detect a difference of 0.15 between the group proportions of 0.40 and 0.25 at a significance level (alpha) of 0.05 using a two-sided z-test with continuity correction. These results assume that 3 sequential tests are made using the O'Brien-Fleming spending function to determine the test boundaries (see also section 8.5 for details on interim analyses). Accounting for a drop-out rate of about 10%, a total of 380 patients needs to be randomised.
9 CONCOMITANT SCIENTIFIC PROJECTS

9.1 Posttraumatic Stress Disorder (PTSD) / Health-related Quality of Life (HrQoL)

PTSD is a stress-related psychiatric disorder that may occur after exposure to extreme trauma and critical illness. PTSD is frequently associated with a compromised HrQoL. It is estimated that about 39% of patients with septic shock suffer from PTSD and impaired HrQoL [SCHELLING 1999]. According to DSM-IV criteria, the traumatic event has to be a catastrophic stressor outside the range of usual human experience, and should be perceived as traumatic by nearly everyone [AMERICAN PSYCHIATRIC ASSOCIATION 1994]. With respect to ICU settings, characteristic burdensome situations are anxiety, hallucinations and paranoia, severe sleep disruption, and communication difficulties [WEINERT 1997]. Individuals who developed PTSD suffer from 3 distinct types of symptoms: re-experiences (flash backs), persistent avoidance of stimuli, and hyperarousal [AMERICAN PSYCHIATRIC ASSOCIATION 1994].

Memory of the traumatic event is an essential part of the pathophysiology. There is evidence that memory or recall of real events during the ICU-stay, even though they are unpleasant, may be protective with regard to anxiety and PTSD. In patients who developed PTSD, memories of delusions are prominent [JONES 2001].

Several studies indicate that in patients with PTSD, imbalances of the hypothalamic-pituitary axis may play a role [RAISON 2003]. Indeed, there is an association between low serum cortisol values, adrenal dysfunction, impaired pituitary ACTH-release, and increased levels of hypothalamic corticotropin releasing hormone and the development of PTSD. This concept is further supported by the observation, that patients who received hydrocortisone for septic shock had a significantly lower incidence of PTSD than patients who did not receive steroids [SCHELLING 2001]. Furthermore, several case reports indicate that application of low doses of hydrocortisone attenuated the intensity of PTSD in victims of violence [AERNI 2004]. In a recent randomised controlled trial, the use of stress doses of hydrocortisone in high-risk cardiac surgical patients reduced peri-operative stress exposure, decreased chronic stress symptoms, and improved health-related quality of life at 6 months after cardiac surgery [WEIS 2006].

It is currently unknown, how cortisol may protect from PTSD. The effect can possibly be explained by a differential influence of cortisol on memory. Increased serum cortisol levels not only result in consolidation of emotional memory but are also known to cause a temporary impairment in memory retrieval which appears to be independent of glucocorticoid effects on memory formation. Disrupting retrieval mechanisms with glucocorticoids during critical illness may therefore act protectively against the development of PTSD by preventing recall of
traumatic memories [SCHELLING 2002]. This is supported by animal experiments, in which pre-treatment with cortisol reduced the memory to a traumatic event. Another explanation is that cytokine-induced brain damage is attenuated by cortisol. However, some data indicate that high doses of glucocorticoids have the opposite effect and lead to a volume reduction of the hippocampus. The link between hippocampus reduction and PTSD in humans is a controversial issue [BREMNER 1995].

Our hypothesis is that early application of dHC in severe sepsis has a positive effect and reduces the incidence of PTSD. To investigate this important question, we will use a panel of validated questionnaires for rating patients at the time of hospital discharge and after 6 months after hospital discharge. It is assumed to have a lost to follow-up either by reduced compliance or death of the patient. It is recognized that avoidance of recall may be a symptom of PTSD, therefore, contact and information of the patient about the questionnaires at hospital discharge is important and may increase the compliance for follow-up. For follow-up at six months after hospital discharge, the coordination center at the Charité will provide the material including stamped envelops to the site investigator who will contact the patient and forward the material to the patient. The questionnaires will be resent to the investigator who will forward the pseudonymised questionnaires to the Charité.

Results of the PTSD and HrQoL questionnaire will not be recognized for the interims analyses or final analysis, because both would be delayed due to the six months gap. Furthermore, it is essential that the questionnaires are validated by a specialist for psychology. All questionnaires will be sent to the Coordinating Investigator and forwarded to the PTSD study-team. Data input in special score-related software sheets will be performed by a study assistant together with a student, and controlled by the psychologist (Dr. Claudia Denke) upon validation and analysis. Statistical analysis will be performed by Dr. Denke in cooperation with the KKSL/IMISE.

The following questionnaires will be used:

- PTSD will be evaluated with the Posttraumatic Diagnostic Scale (PDS) [FOA 1997].
- HRQoL will be evaluated with the self-administered Medical Outcomes Study Short Form Survey (SF 36) [MChorney 1993], German version: [Bullinger 1998]
- QUALY (Quality Adjusted Life Years) will be evaluated with Euro-Quol [The Euro-Qol Group 1990].
- Anxiety disorder and depression will be evaluated with the German Version of Hospital Anxiety and Depression Scale (HADS) [Herrmann 1995].
- Sociodemographic data will be evaluated with a non-validated set of questions.
9.2 Transcriptomics / Proteomics

Modulation of transcriptomic and proteomic response to severe sepsis by corticosteroids

To systematically assess the molecular mechanisms underlying the beneficial effects of IdoHC, we propose to study gene expression patterns in leukocytes and plasma proteomic response to severe sepsis with or without administration of hydrocortisone. A total of 4868 transcripts will be systematically analysed using the SIRS-Lab GmbH in-house research microarray to reflect transcriptional activation and/or suppression by sepsis as well as its modulation by corticoids. Since our previous results in patients with SIRS due to coronary artery bypass grafting with or without cardiopulmonary bypass indicate that gene array and multiplex protein analysis, only in concert, can illuminate the molecular mechanisms underlying the host response, we will combine the analysis of a medium density array to assess a broad spectrum of inflammatory transcripts with multiplex cytokine analysis. Ideally, transcriptomic analysis would be combined with large scale proteomic profiling. Thus the decision to include multiplex cytokine analysis rather than a broader proteomic assessment reflects a compromise to limit costs while assessing the most significant inflammatory signalling molecules in a comprehensive fashion. This approach has been demonstrated to give valuable insights as it allows to address the source of the cytokine response and/or to characterize the inflammatory phenotype of circulating immune competent cells (1).

Transcriptomal analysis

Microarrays will be run for all patients at the defined time points. For this purpose and to assure reproducible results among the various SepNet centers, PAXgene tubes (Qiagen, Hilden, FRG) will be used for leukocyte sampling under controlled venous stasis (<30s, 40 torr) and total RNA isolated according to the manufacturer’s instructions. RNA purity will be confirmed by spectrophotometry (A260/A280 > 1.6, A260/A230 > 2.0), ethidium bromide-stained RNA agarose gel, and a multiple exon-spanning real-time PCR (RT-PCR) amplification of a housekeeping gene (GAPDH). Experiments will be performed using the SIRS-Lab GmbH in-house research microarray which comprises 5308 probes addressing 4868 transcripts corresponding to 3704 human genes relevant to inflammation, immune response and related processes as well as 78 reliable control probes.

10 μg total RNA will be reverse transcribed using Superscript-II reverse Transcriptase from Invitrogen (Karlsruhe, FRG) in the presence of aminooallyl-dUTP from Sigma and labeled using the AlexaFluor 647 system. AlexaFluor 647-labeled cDNA will be co-hybridized with AlexaFluor 555-labeled cDNA obtained from the same amount of total RNA isolated from the immature monocytic cell line SigM5 obtained from ATCC. This approach allows for standardized
comparison of data derived from different hybridization experiments, which is a crucial factor in the light of the high number of assessed patient days. After incubation in a hybridisation apparatus (HS 400, TECAN, Crailsheim, FRG, for 10 h at 42 °h, formamide-based hybridisation buffer system) arrays will be washed according to manufacturers instructions, dried and hybridisation signal intensities will be measured using an Axon 4000B scanner (Axon Instruments, Foster City, CA). All required materials and the technical equipment is available at the laboratories of the Klinik für Anästhesiologie und Intensivmedizin of the Friedrich-Schiller-Universität or its spin-off SIRS-Lab, GmbH, Jena.

Microarray data pre-processing of hybridisation signals will include i) spot detection and background subtraction, ii) spot flagging according to defined signal-to-noise threshold values, iii) normalization and transformation of the signals obtained from different channels as described in detail [TOMIC 2005]. PAXgene tubes are provided to the sites. After blood collection, the tubes will be stored at least at -20 °C until transfer to the central blood storage bank (see 9.4), which forwards the tubes in batch to the SIRS-Lab GmbH.

**Multiplex cytokine analysis**

Serum samples for cytokine analysis will be obtained, prepared, stored, and transferred to the central blood bank as described in 9.4. The Multiplex bead kit from BioRad Laboratories, Inc. (Hercules, CA, USA), which includes cytokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-17, TNF-α and IFN-γ), growth factors (G-CSF, GM-CSF) and chemokines (MCP-1 and MIP-1β) will be used. Standard curves for each mediator will be generated from 2 to 8000 pg/ml. 50 μl of undiluted serum samples will be incubated with 50μl of antibody-coupled microsphere sets (5000 beads per mediator per well) for 1 hour at room temperature. 25 μl of freshly diluted secondary detection antibody (1μg/ml) will be added and incubated at room temperature for 1 hour. 50 μl of streptavidin-PE (1x) will be added, followed by incubation for 10 minutes at room temperature. After each step (incubation of samples with microsphere sets, incubation with secondary detection antibody and streptavidin-PE), a filtering and three washing steps using a vacuum manifold will be performed. Thereafter, 125μl of assay buffer will be added to each well and analysed on a Bioplex™ Protein Array System (BioRad Laboratories, Inc., Hercules, CA, USA) according to the manufacturer's instructions.

**Statistical Analysis**

*Microarray data:* In the analysis, reliable probe sets will be included, i.e. probes with sufficient mean spot quality and with robust expression variation throughout the experiment. Missing values will be imputed employing the k-nearest neighbour algorithm [TOMIC 2005].
Comparisons will be performed applying appropriate statistical approaches: Expression of transcripts in severe sepsis prior to randomisation into placebo or IdHC arms (unpaired t-test, ‘gene by gene’); changes over time in severe sepsis depending on progression to septic shock or not in patients receiving IdHC or placebo (two dimensional one-sample principal component (pc)-test will be assessed. In order to control the false discovery rate (FDR) occurring in multiple comparisons, a vector of q-values will be estimated for each vector of p-values. Selected genes will be ordered by hierarchical cluster algorithm using correlation distances and the average linkage method [SIMON 2003,TROYANSKAYA 2001,LÄUTER 1996,STOREY 2003].

Expected results

Anti-inflammatory strategies, most notably IdHC might limit untoward effects of activation of the host response but might also result in impaired wound healing and immunodeficiency, giving rise to infectious complications, such as candidemia. This might limit the potential of IdHC in prophylaxis of shock in severely septic patients. Synoptic view of data derived from a multitude of „single-gene-experiments“ or studies addressing a few inflammatory markers would suggest that IdHC modulates the systemic inflammatory response in septic shock in a complex manner and is by no means a simple anti-inflammatory agent [KEH 2003]. Gene expression analyses in human non-septic mononuclear cells indicate that glucocorticoids in doses used in the clinical setting may stimulate innate immune responses [GALON 2002]. Clinical data regarding modulation of the inflammatory profile of expressed transcripts of circulating cells in patients with severe sepsis are sparse or absent.

„Single gene“-approaches are inherently limited to assess such complex pathophysiological networks most notably in the light of the current understanding of confounding genetic factors, such as polymorphisms in inflammation-related genes. Thus, the analysis of this complex, partially redundant but also antagonistic pattern of transcriptional activation or suppression requires novel tools to assess a broad spectrum of interacting genes in a multiplexed manner in combination with sophisticated data pattern recognition [GREGERSEN 2003,PRUCHA 2004]. These techniques may not only allow a better understanding of the pathophysiology but may lead - similar to what was observed for myeloid leukaemia [BULLINGER 2004] to individualised therapy for the benefit of patients (“theragnostics”) in the systemic inflammatory response to infection of various degrees of severity, most notably severe sepsis and septic shock.
9.3 Immunomonitoring (HLA-DR on monocytes and functional assays)

Sepsis is characterized not only by Inflammation, but also by an anti-inflammatory reaction. The anti-inflammatory response reflects the normal response to stress and protects the host from overshooting inflammation; however, if anti-inflammation predominates for a prolonged time, this may be harmful either and may lead to incapacity of the immune system to respond adequately to stress and infection [MUNFORD 2001]. Cortisol is critically involved in the anti-inflammatory response to stress; on the other hand, cortisol is also essential for protection against infection. In this setting, exogenous application of glucocorticoids may potentially be associated with unwarranted immunosuppressive effects. However, the dose and time of application plays an important role. Indeed, low HC application in patients with septic shock has not been associated with an aggravated immunosuppressive reaction [KEH 2003, OPPERT 2005]. In contrast, studies with high doses of glucocorticoids when administered for a short period failed to improve outcome (see introduction). Data about immune responses in patients with severe sepsis treated with low HC are missing. In HYPRESS, HLA-DR expression on monocytes, endotoxin tolerance, and the TH1-Th2-balance will be monitored in selected sites in Berlin (immediate sample processing is necessary)

The expression of HLA-DR receptors on circulating monocytes is increasingly used to investigate the capacity of monocytes to initiate adaptive immune responses. Studies indicate that a severe depression of HLA-DR is associated with an increased risk for development of infections and a poor outcome in patients with severe sepsis or septic shock [VOLK 2002, STROHMEYER 2003, LEKKOU 2004, TSCHAIKOWSKY 2002, MONNERET 2004, HYNNINEN 2003]. There is a correlation between the severity of sepsis and HLA-DR depression. Interleukin 10 seems to play a major role in immediate receptor internalization [FUMEAUX 2002]. Recent data indicate that HLA-DR receptor regulation is disturbed at the transcriptional level as well, and that prolonged depressed transcriptional regulation is associated with a poor outcome [PACHOT 2005]. Furthermore, non-survivors of septic shock often have the highest cortisol values and lowest HLA-DR expression, indication a role of endogenous cortisol in receptor regulation [LE TULZO 2004].

Another parameter for impaired immunocapacity is the release of TNF after stimulation of monocytes with endotoxin (LPS tolerance). Low production of TNF-α by monocytes was found to predictive for poor outcome in sepsis and a risk factor for development of infections [MUNOZ 1991, WEST 2002]. Some data indicate that immune augmentation with interferon-γ or granulocyte monocyte stimulating factor improve both, HLA-DR expression and monocyte
function [DOCKE 1997, NIERHAUS 2003]. Data about TNF-α release by monocytes in patients with severe sepsis who have been treated with IdHC are missing.

Glucocorticoids are known to promote proliferation of TH-2 cells [RAMIREZ 1998]. Th-2 cells release anti-inflammatory cytokines (e.g. IL-10) and associated with immunosuppression in sepsis; Th-1 cells release e.g. IFN-γ and promote inflammation [HOTCHKISS 2003]. Interestingly, in patients with septic shock, IdHC treatment was associated with increased plasma levels of interferon-γ and a depressed production of IL-10 [KEH 2003]. However, in vitro tests in Concanavalin-stimulated (ConA) lymphocytes have not been performed in this study, thus the source of increased INF-γ production remains speculative. Results of the Corticus immune sub-study may provide additional information in patients with septic shock.

Immunomonitoring of the depicted parameters has to be done immediately after blood sampling. Blood samples (5 ml EDTA-plasma and 5 ml Serum monovettes, Sarstedt) will be collected at baseline, an on days 2, 4, and 6. Blood samples will be stored on ice until processing. This part of the immunologic add-on project can only be performed in centers which are close to a laboratory, i.e. only in Berlin centers. The measurements in HYPRESS will be performed by the Immunology Working Group of the Department of Anesthesiology and Intensive Care Medicine. SOPs have been established and used in the Corticus trial. The immune project will be done in cooperation with the Institute of Medical Immunology Campus Charité Mitte (Prof. Volk).

HLADR-expression will be measured in heparinized blood using QuantiBRITE™ Anti-HLA-DR-Phycoerythrin/Anti-Monocyte PerCP-Cy5.5 Test-Kit (Becton Dickinson). This standardized test allows quantitative receptor evaluation on single cells and is independent from variations of cytometer settings. LPS-tolerance is measured by LPS-stimulation of whole blood. The supernatant containing IL-6, IL-10, and TNF-α is measured by ELISA. TH-2 proliferation is measured in ConA-stimulated whole blood, and the ratio of TH-1 and TH-2 cells by evaluation of the ratio of IL-10 and IFN-γ. Additionally, nitrite/nitrate serum will be measured by Griess reaction to gain information about inhibition of NO-formation by IdHC (for rationale see above).

Immunomonitoring in HYPRESS will provide important information of possible immunosuppressive effects. Although there is currently no evidence that IdHC treatment is associated with severe immunosuppression, it is important to recognize that there are no data available in patients with severe sepsis who are not in shock.

9.4 Serum-, Plasma- and DNA- blood sample storage bank

Early studies of genomic markers in selected patient populations showed an association between mediators (e.g. tumor necrosis factor) and increased mortality and incidence of severe sepsis, respectively. Similar results could be confirmed in subsequent trials with different patient
populations [TANG 2000, MIRA 1999, MENGES 2001]. For example, sepsis morbidity and mortality was associated with genomic polymorphism (single nucleotide polymorphisms [SNP]) of coagulation system genes [MENGES 2001]. However, most of the studies had low sample sizes and poor statistical power, complicating the interpretation of results with respect to the association between the genetic and clinical phenotype in subgroups. It is the goal of the SepNet blood sample bank to evaluate genotyping SNP in severe sepsis relevant genes under control of the genomic variability by typing of definite non-candidate SNP (concept of ‘genomic controls’). Therefore, DNA-, plasma, and serum blood specimen will be stored in the SepNet sample bank to evaluate polymorphisms of inflammatory mediators (e.g. TNF-α, tissue factor pathway inhibitor) as prognostic markers in severe sepsis. To better understand the clinical relevance of genotyping in a complex network, it is critical that interactions between the clinical course and protein polymorphisms, protein expression, and protein interactions are considered. These investigations will be performed later.

Beyond genotyping, continuation of the blood sample bank is of extraordinary value to identify and validate new biomarkers. Modern methods of proteomics may play an important role in defining biomarkers which allow early diagnosis of sepsis and early therapeutic intervention. One promising approach is the multi-parameter analytics, which allows the analysis of hundreds or thousands of parameters to improve predictive, preventive, and individual diagnostics to anticipate the beginning of sepsis, the clinical course, stratification, and the efficacy and side effects of therapeutic interventions [WESTON 2004].

One example for these new methods is mass spectrometry like SELDI-TOF. First experiments show, that this method, by comparing protein spectrums, has a high sensitivity and specificity to distinguish patients with non-infectious SIRS from patients with infectious SIRS (sepsis) [KIEHNTOPF 2003]. It can be assumed that not only the stage of a disease but also different therapeutic interventions influence the protein spectrum. The characterization of differentially expressed proteins in patients with improved outcome due to specific therapeutic interventions may lead to the identification of biomarkers which allow early intervention of high risk patients before the development of severe stages of illness.

For all these multi-parameter assays and future innovative methods, it is the prerequisite that blood sampling and storage is performed in multiple centers on a high technical standard. Especially in multi-center trials, blood sampling is accident-sensitive which may reduce the quality of results. One reason is the difference in pre-analytic procedures in different sites. It is therefore necessary to ensure standardized blood sampling and storage procedures; this is only possible by a centrally organized blood sample bank. In recent trials of the SepNet, standards for blood collecting, quality of blood samples, blood sample processing, and storage have been successfully defined.
Thus, to ensure adequate blood collection and quality of pre-analytic procedures, SOPs for blood sampling will be provided to the centers. The serum, plasma, and DNA probes will be stored in the SepNet Central Blood Sample Storage Bank for identification of and validation of future biomarkers of sepsis.

The required primary tubes (monovettes), secondary tubes (storage tubes), and special blanks will be provided to the sites. To avoid confusion, each blood sample will be assigned to a blank with an unique code number ('Probennummer', order number). Each blank contains barcodes, which has to be affixed to the corresponding primary and secondary tubes after blood collection. In addition, the date and time of blood collection is recorded on the blank.

The plasma tubes are then centrifuged at 2000g for 10 minutes at 20°C (preferred temperature) in a centrifuge with cooling system. The serum tubes are stored at room temperature for 30 minutes until clotting, and then centrifuged at 2000g for 10 minutes at 20°C (preferred temperature) in a centrifuge with cooling system. Afterwards, the serum and plasma supernatants are transferred with a pipette to the barcoded secondary tubes (serum with brown colour label, plasma green colour label), and immediately frozen at least at -20°C.

Blood samples for DNA-extraction (4,9 ml EDTA-monovettes) are stable at room temperature for several days and will be sent to the central blood sampling bank without prior centrifugation and freezing. Each DNA-sample will be affixed to an unique barcode from a special blank for DNA-blood samples. This blank for DNA-samples contains neither the patient name nor the patient number. For DNA-samples, the patient number, the number of the blank (DNA-sample number) and the patient sticker of the site containing individual information including the address will be affixed to another special DNA-blank and faxed to a trustee. After receiving a notice of receipt, this special DNA-blank with the patient information has to be destroyed immediately. The DNA-sample will be sent to the central blood-sampling bank together with the DNA-blank, which contains only the date and time of blood sampling.

Serum and plasma probes will be collected every three months by a special courier on dry ice and transferred overnight to the central blood sampling storage bank. EDTA-probes for DNA will be sent by regular mail. For this, the sites will be provided with labelled T-boxes and prepared tubes for sending. DNA will be collected only once for each patient.

Blood probes received from sites will be controlled according to the above described criteria and identified by a barcode reader which information is then stored in the laboratory information system. The frozen probes will then be sorted. After sorting, all probes of one patient will be unfreezed under standardized conditions. Afterwards, aliquots of the serum and plasma probes will be prepared by an automatic system. Serum and plasma probes will be transferred to tubes which contain a unique identifier at the bottom for a 96-well storage plate. Each rack contains 96 probes, and each rack may be identified by an unique barcode.
10 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

All trial participants consider conducting the study in accordance with local laws and ICH guidelines for Good Clinical Practice (GCP) issued in June 1996 and CPMP/ICH/135/95 from September 1997, taking into account the Declaration of Helsinki and all its revisions.

10.1 Initial Submission

10.1.1 Qualification of investigators and trial sites

Prior to the initial submission to the ethics committees (EC) each centre that wants to participate in the trial must submit proof of qualification and experience of trial personnel and appropriateness of the trial site according to §7(2) and §8(5) German GCP-laws (GCP-V). To this purpose, the principal investigator has to make available to the sponsor (represented by the Coordinating Investigator) the following documents:

Investigator:

- Dated and signed CV including: Name, address of service facility, recent job title, professional development, additional qualifications, track records of former clinical trials (number, phases, indication).
- If available: publication list, certificates of qualifications.
- Confirmation of knowledge of ICH-GCP Guideline, requirements AMG and GCP-V (knowledge of protocol, IB, definitions of AE/SAE, notification requirement, Archiving, requirements regarding monitoring, audits and inspections etc.).
- If available, results of monitoring, audits and inspections already done.
- Dated and signed financial disclosure.

Trial sites:

Information about personnel availability: Number of staff, function and qualification (education, experiences in clinical trials, training) thereof, description of trial related tasks delegated.

Appropriateness and certificate of qualification

- Main focus of treatment in the trial site.
- Number of patients (e.g. per year) of the required indication.
- Information about competing trials.
Infrastructure: description of the facility

- Finances and technical devices required for the trial conduct.
- Availability and experiences/qualification in emergency care.
- Availability and connection to emergency unit of a hospital (e.g. medical practice).

10.1.2 Submission to the leading ethics committee and competent federal authority

Prior to submission of the trial related documents to the leading ethics committee and the competent federal authority the sponsor (represented by the coordinating investigator) is responsible to enter the trial into the European database of clinical trials (EudraCT). After the web based entry the sponsor will be issued a EudraCT number which must be submitted with all future documents.

Afterwards, the protocol and all other associated documents according to GCP-V §7 will be submitted to the leading ethics committee responsible for the coordinating investigator for approval. In addition to the required documents from each investigator the coordinating investigator must provide evidence of at least two years experience in clinical trials.

Parallel to the submission to the leading ethics committee each participating EC also receives a copy of all submitted documents including information about trial sites and investigators (see above) in their field of responsibility. This documentation should be used by the EC for evaluation of the appropriateness of the trial site.

At the same time the study documents will be submitted to the competent federal authority (BfArM) according to the requirements of GCP-V §7.

Only following a positive review by the leading ethics committee and approval from the competent federal authority the trial can start.

The written approval of the EC must be filed in the trial master file (TMF). Additionally, every participating centre must receive a copy of these documents to be filed in the investigator site file (ISF).
10.2 Submission of Protocol Amendments

According to GCP-V§10, the leading ethics committee and the competent federal authority are to be informed on any protocol amendments. In case of substantial changes, a new positive review of the leading ethics committee and approval of the BfArM are required, before the changes become effective. Changes that require approval and positive review by the ethics committee include:

- Changes that may have an effect on patient safety, e.g. essential changes in the therapeutic or diagnostic procedures.
- Changes concerning the risk-benefit considerations.
- Additional data collection or statistical evaluations that necessitate changes in the informed consent form.
- New scientific data leading to changes in rationale or expected significance of the trial.
- Significant changes concerning leadership or conduct of the trial.
- Changes concerning the quality or the innocuousness of the investigational drug.
- Clinical trials with drugs, containing genetically changed organism: changes concerning the risk-benefit considerations.

10.3 Committees

10.3.1 SepNet Steering Committee
The HYPRESS SepNet Steering Committee will be responsible for setting up, running, evaluating and reporting the results of the study. It is responsible for continuing or ending the study for efficiency or safety reasons. The steering committee supports quality performance of the study and helps with problems that arise during the study.

10.3.2 Data Monitoring Safety Board (DMSB)
The DMSB is an independent data-monitoring committee. The DMSB will assess at intervals (interim analyses) the progress of the trial, and will evaluate safety data and critical efficacy endpoints. The DMSB will recommend to the SepNet Steering Committee whether to continue, modify, or stop the trial. The DMSB will receive the results of the planned interim analyses and safety analysis.
11 DATA HANDLING AND RECORD KEEPING

11.1 Case Report Form (CRF)

Final documentation of all study relevant data is performed via remote data entry into a web-based electronic (e)CRF. The eCRF is computerized by the KKSL data management team. A manual for eCRF handling will be provided to the trial sites in a paper format.

Documentation of source data is performed in two ways:

- All source data which are part of routine patient care (e.g. laboratory values, hemodynamic parameters, vital signs, medication, microbiology etc.) are documented in the patient medical record. Data entry in the eCRF is performed from the source data which remain in the patient medical record.
- Source data for PTSD and HrQoL are documented on provided forms (questionnaires). The originals are send to the Charité study team, a copy is stored in the investigator site file.

Data entry into the web-based eCRF is performed by the investigator at the trial site or authorized person via an internet-connected computer. The principal investigator or one of the investigators will review the eCRF for completeness and accuracy, sign and date all relevant eCRF pages and any changes therein. In case of a major correction or missing data, the reason for it shall also be given. The investigator must assure completion, review and approval of all eCRFs. At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the eCRF. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

The eCRF should be completed in real-time but not later than 2 weeks after study day 28 for all data obtained until day 28. Follow-up data after day 28 may be completed later.

11.2 Data Collection and CRF Items

The eCRF consists of different sections for inclusion, baseline, treatment, follow-up, premature termination, and summary with following items besides others:
11.2.1 Inclusion

**Patient identification list (Investigator Site File)**

The patient identification list contains the personal data such as the name, gender, date of birth, and the corresponding MedKit-ID and patient-ID (pseudonym) of all included patients. The list is NOT part of the eCRF but has to be stored in the investigator site file. The list has NOT to be transmitted to anybody but remains at the site. The list enables identification of patients by the pseudonym for later queries.

**Screening**
- Patient inclusion
- Reasons for non-inclusion

**Inclusion**
- Informed consent (date, time, patient, legal representative, proxy, preliminary by medical consultant)
- Time of inclusion
- Inclusion / exclusion criteria

**Randomisation**
- Randomisation sheet
- Assigned Patient-ID

11.2.2 Baseline

**Baseline**
- Demographic data (gender, age, weight, height)
- Date of ICU admission
- Main diagnosis of ICU admission
- Concomitant diseases
- Concomitant medication
- Etomidate history
- Glucocorticoid history
- Recent medical history
- Source and localisation of infection
- Microbiological results
- Time severe sepsis started
- Organ dysfunctions
- Hemodynamic and vital parameters
- CVP, SAP, DAP, MAP, ScvO₂, HR, Temp
  - Mechanical ventilation / pulmonary parameters
    - PaO₂/FiO₂, respiratory rate, PEEP, tidal volume, plateau pressure
  - Catecholamines, vasopressors
  - Routine laboratory values
  - Items for calculation of SOFA, SAPS 2, SAPS 3, APACHE II, ICAM-ICU, RASS
  - Fluid intake, insulin requirement
    - ACTH-test, study specific blood samples

Note: Hemodynamic variables and volume status is recorded at 6 and 24 h after onset of severe sepsis. The time period may overlap with treatment pages, when patients are included in the study early after onset of sepsis.

11.2.3 Treatment (Study days 1-14)

- Application of the study medication
- Occurrence of septic shock
- Catecholamines, vasopressors
- Concomitant medication and treatment
- Hemodynamic and vital variables
- Mechanical ventilation / pulmonary parameters (see above)
- Laboratory data
- Single items for calculation of SOFA, GCS, MRC, ICAM-ICU, RASS
- Insulin requirement
- Fluid intake
- Renal replacement therapy
- Mechanical ventilation
- Safety issues
- AEs/SAEs
- Survival status at the end of treatment

11.2.4 Follow-up

Study day 28

- Survival status
- Occurrence of septic shock
- Days mechanical ventilation
- Days renal replacement therapy
- Safety issues
- MRC, ICAM-ICU, RASS
- AEs/SAEs

**ICU discharge**
- Date of discharge
- Survival status at discharge
- Safety issues
- MRC, ICAM-ICU, RASS
- Days mechanical ventilation
- Days renal replacement therapy

**Hospital discharge**
- Date of discharge
- Survival status at hospital discharge
- PTSD/HrQoL questionnaire
- Informed consent for 180-day PTSD/HrQoL questionnaire

**90 and 180 days after randomisation**
- Survival status

**6 Months after hospital discharge**
- PTSD/HrQoL questionnaire

**11.2.5 Premature termination**

**Termination of study drug application before day 11**
- Septic shock
- Lost to follow-up (discharge)
- Therapy with open label hydrocortisone
- Other reasons for termination of study drug application

**Premature termination of the study**
- Withdrawal of informed consent
- Informed consent can not be obtained
• Lost to follow-up
• SAE
• Others

NOTE: PTSD and HrQoL items are not part of the eCRF.

11.3 Data Management

Remote data entry via the internet is performed with the software ‘eReasearch Network’ which consists of different modules. The module ‘eResearch eDatamanagement’ is the platform for configuring the eCRF and for creating a database (Oracle-DBMS) to which the data are transferred. The data transfer is performed by a mask created with the module ‘eResearch Screen Modeller’.

Data entry into the web-based eCRF is performed via the internet. Authentication of the investigator is performed by login and password. All data transfer between the client and server is coded (HTTPS). The server is placed in a secured room and electronically protected by a double firewall within the KKSL network. A data-backup is performed several times a day. The backups are secured in a separate room which is accessible to the system administrator only. Unauthorized access to the data protected by a hierarchic security procedure. All data remain anonym during analysis.

The KKSL data management team has access only to pseudonymous data of the eCRF. The allocation between the individual patient and Patient-ID is not transferred to the KKSL and remains at the trial site.

Quality control of data entry is performed in different ways. At the study site, data entry is checked for plausibility by the eCRF software, which allows immediate completion or correction of false or missing data. At the KKSL, data are checked again for consistency and plausibility. If there are queries, these data are marked for the investigator in the eCRF. Any corrections can only be made by the person who had performed the first data entry. Any changes of data are recorded in an audit trail for tracing.

Once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between the coordinating investigator, the biometrician and the data manager.
11.4 Archival

The investigators have to arrange the retention of the subject identification codes for at least 15 years after the completion or termination of the trial. Patient files and other source data shall be kept for the maximum period of time permitted by the hospital.

The coordinating investigator or other owner of the data shall retain all other documentation pertaining to the trial for at least 10 years. These procedures shall include:

- The protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product used.
- Standard operating procedures.
- All written opinions on the protocol and procedures.
- Interim and final report.
- Case report forms, data base, Audit certificate(s), if available.
- All other relevant documents of the trial master file, according to the ICH-GCP guideline.

Any change of data ownership shall be documented. All data shall be made available if requested by relevant authorities.
12 REFERENCE EVALUATIONS

12.1 Cortisol Measurement

Although there is no real consensus how to define adrenal insufficiency in septic shock, there is strong evidence that adrenal dysfunction plays a major role in septic shock. It is unknown at what time adrenal insufficiency develops and whether sepsis-induced hypotension is a hallmark of adrenal insufficiency. Indeed only about 75 % of patients with septic shock had been non-responders in the French study, and preliminary data from the CORTICUS study indicate that the incidence of adrenal insufficiency was even lower (about 40 %). It is currently debated whether ldHC is only effective in patients with proven adrenal insufficiency, and one meta-analysis concluded that this is not the case [MINNECI 2004].

There are no data available about adrenal function of patients with severe sepsis who are not in shock. In the study by Confalonieri, adrenal function was not investigated [CONFALONIERI 2005]. One might hypothesize that the positive effects observed in this study were rather due to the anti-inflammatory effects and inhibition of NF-kB-dependent pathways in the sense of a relative cortisol deficiency during profound inflammation. It is extremely unlikely that the study was biased by assignment of patients with adrenal insufficiency to one treatment arm only. However, it is an unique opportunity in HYPRESS to investigate adrenal function at the onset of severe sepsis, and to gain data whether the effects of ldHC in severe sepsis depend on adrenal function. The results will have major impact on the clinical practice of adrenal function tests in severe sepsis. The planned assays will measure total cortisol at baseline, cortisol after ACTH-stimulation, and calculated free cortisol. Based on the current knowledge, non-responders will be defined as a cortisol increase of ≤ 9 μg/dl. If the results of ongoing investigations come to modified definitions of adrenal insufficiency, this will be recognized for the final analysis. Cortisol will be measured in the central reference laboratory in Munich by Dr. Michael Vogeser. Prof. Josef Briegel will be responsible for coordination of the measurements, shipping and logistic, and data reporting of cortisol values to the KKSL.

The cortisol measurement has to be performed centrally for the following reasons: Preliminary data from the CORTICUS sub-study on cortisol harmonization have shown that there is a considerable variation between different cortisol assays when cortisol was measured in local laboratories. In addition, about 20 % of patients were designated falsely as responders or non-responders when the cortisol values were compared to values measured by the gold standard method. As the gold standard for cortisol determination in serum, the LC-tandem mass-spectrometry (LC-MS/MS) method (Isotope-Dilution-Liquid Cromatography Electrospray Ionization Tandem Mass Sprectrometry with On-line Extraction) has been established in the
reference laboratory [VOGESER 2001]. This method had been proven to be linear (0-55 μg/dl cortisol, r=0.999) and precise (total coefficient of variation between 5.0% and 3.2% at a mean cortisol concentration of 1.5 μg/dl and 27 μg/dl, respectively). In addition to the gold standard method, cortisol will be measured by Electro-Chemo-Luminescence-ImmunoAssay (ECLIA, Roche Diagnostics). Comparative measurements depicted that this assay had the lowest variation, however, there had been as in other assays a trend for overestimating cortisol compared to LC-MS/MS. Nevertheless, the goal is to produce clinically relevant data, which will probably allow decision making due to test results. Since the LC-MS/MS method is available only in specialized centers, it seems to be of critical importance to compare the obtained values to an assay, which can be performed everywhere.

12.1.1 ACTH-test
The ACTH-test is performed with 250 μg cosyntrpin (Synacthen®, Novartis).
To perform the ACTH-test, two blood samples are required, one before administration of cosyntrpin, and one 60 min after administration of cosyntrpin. After obtaining a 5 ml blood in a serum tube, 250 μg of cosyntrpin (diluted in 10 ml of normal saline) is administered intravenously; after 60 min the second blood sample is obtained.
The required primary tubes (monovettes), secondary tubes (storage tubes), and special blanks will be provided to the sites (see chapter 9.4).
The serum tubes are stored at room temperature for 30 minutes until clotting, and then centrifuged at 2000g for 10 minutes at 20°C (preferred temperature) in a centrifuge with cooling system. Afterwards, the serum supernatants are transferred with a pipette to the barcoded secondary tubes and immediately frozen at least at -20°C. The serum probes for cortisol measurements will be collected every three months by a special courier on dry ice and transferred overnight to the central blood sampling storage bank, and will be forwarded in batch later to the laboratory in Munich.
NOTE: If the ACTH-test can’t be performed for any reason, the start of study medication should not be delayed. Patients without an ACTH-test are not excluded from the study. The ACTH-test is performed in at least 100 patients. Synacthen® has to be provided by the sites and is reimbursed by case payment.
13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Direct Access to Source Data

According to ICH-GCP and to the applicable German laws, the principal investigator must permit all authorized third parties access to the trial site and insight into the medical records of the trial subjects (source data). This permission includes the clinical trial monitors, auditors and other authorized employees of the sponsor, as well as members of the local or federal authorities. All these persons are sworn to secrecy.

13.2 Monitoring

To ensure the quality of the trial, on-site monitoring will be performed by staff of the KKSL or delegates. At beginning of the trial, initiation-visits will be performed. During the trial, for-cause monitoring, depending on the quality of data and adherence to the protocol, will be performed. During monitoring, all study-relevant documents will be controlled and up-dated if necessary. The investigators will ensure access to all study-relevant facilities, source data, and the study medication. The amount of source data verification will be defined in the monitoring manual. A guideline for monitoring will be based on SOPs of the KKSL and described in detail in a monitoring manual.

13.3 Audits

In order to guarantee that the conduct of the study is in accordance with ICH-GCP and the national laws, the sponsor reserves the right to audit selected trial sites. The auditor will be independent from the staff involved in the proceedings of this clinical study. The investigator agrees to give the auditor access to all relevant documents for review.

13.4 Inspections

According to the German drug law (AMG) and the corresponding GCP-ordinance (GCP-V), inspections of the trial sites may be performed by the local or federal authorities at any time during or after completion of the trial. The investigator agrees to give the inspectors access to all relevant documents for review.
14 DATA PROTECTION

For conducting the trial, it is necessary to collect medical data and personal data of the trial subjects. Personal data of the trial subjects (name, date of birth) are documented in the patient identification list together with the patient-ID (pseudonym). The list remains at the trial site and is strictly confidential and may not be send to anybody. All medical data of a trial subject will be transferred to the KKSL electronically (eCRF) by the internet together with the corresponding patient-ID. The KKSL will not receive any personal data and no data, which may identify the individual patient at any time. However, for conducting queries, it is necessary that the KKSL may link a pseudonym to a trial site.

In the case of withdrawal of consent the stored data will be checked for further use. Data, which are not used any longer, will be deleted immediately.

Collected personal data will be stored in an anonymous manner after finishing of all concomitant scientific projects 10 years at the latest, if there are no other regulatory or contractually archiving periods.

DNA-sample (SepNet central blood storage bank)
The DNA-sample is coded at the trial site with a unique DNA-ID (attached barcode provided by a special DNA-blank) and send to the central blood storage bank. The DNA-ID, personal data, and the pseudonym (patient-ID) are faxed to an independent trustee. After confirmation of receipt, information of the DNA-ID is destroyed at the trial site to ensure that no link is possible between the DNA-ID and patient-ID at the site. That is, the DNA-ID can only be assigned to the patient-ID by the trustee. The trial subject may withdraw consent for using the DNA-sample and any data at any time by information of the trustee only. Analytical results of the DNA-sample are forwarded together with the DNA-ID to the central documentation (KKSL). Before ending of the trial, the central documentation receives no information about the allocation of the DNA-ID to the patient-ID.

Plasma, -serum, and RNA blood samples (SepNet central blood storage bank)
Plasma, serum, and RNA blood samples will be coded at the trial site with unique blood sample IDs (attached barcode provided by special blanks) and send to the central blood storage bank. Some of the coded blood samples will be forwarded later to the central laboratory in Munich (cortisol measurement) or SIRS-Lab GmbH. None of the different laboratories or central blood storage bank will receive personal data at any time. Analytical results are forwarded together with the corresponding pseudonym (patient-ID) to the central documentation.
Plasma and serum blood samples in Berlin sites

Blood samples will be collected in Berlin sites for a sub-study. The blood samples have to be analysed immediately (within hours) in a laboratory of the Charité, i.e. storage of samples is not possible for batch processing. Blood samples will be obtained at the sites by the investigators or assigned staff (e.g. study nurse) and immediately coded with the patient-ID. The coded blood samples will be transported to the laboratory, which receives information only about the patient-ID. All data obtained from analytical measurements will be assigned only to the patient-ID, and all data documented electronically in a database with the pseudonym of the patient only. The database will be stored on a secure server at the Charité, and registered at the data protection commissioner of the Charité Universitätsmedizin Berlin (Dipl.-Phys. Bernd Pilgermann).

PTSD and HrQoL

In the sub-study PTSD and HrQoL, trial subjects will be asked to complete special questionnaires. The first examination will be performed by the investigator at the trial site before hospital discharge. For this examination, the patient will receive an additional information sheet. The patient has to give written informed consent to complete the questionnaires. The completed questionnaires are coded with the patient-ID and no personal data will be send by the investigator to the Charité study team.

To gain valid information, it is necessary to perform the same set of questions 6 months after hospital discharge a second time. This second questionnaire will be centrally organized by the Charité study team. To contact the patient after 6 months, it is necessary, that the patient (or legal representative, or proxy) gives written informed consent. The material with the pseudonym of the patient will by provided to the site investigator who will send the questionnaires to the patient. The patient returns the pseudonymised questionnaires to the Charité study team in a prepared envelop labelled with the address of the Charité study team and the sender address of the corresponding principal investigator of the site. The questionnaires, which are send to the patient, are coded with the patient-ID. The patient will be instructed not to put the name or other personal data on the sheets. Only the patient-ID will be used for electronically documentation and statistical analysis. The pseudonymous database will be stored on a secure server at the Charité, and registered at the data protection commissioner of the Charité Universitätsmedizin Berlin (Dipl.-Phys. Bernd Pilgermann). The Charité study team receives only pseudonymised data, personal data will stored only at the trial site.
14.1 Declaration to Data Protection

During data entry, handling, and analysis at the Koordinierungszentrum für Klinische Studien Leipzig – KKSL, Universität Leipzig, Härtelstr. 16-18, 04107 Leipzig all requirements of the data protection law will be take into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorized access.

During data entry, handling, and analysis of data obtained within sub-studies at the Klinik für Anästhesiologie und operative Intensivmedizin, Universitätsmedizin Berlin, Augustenburgerplatz 1, 13353 Berlin, all requirements of the data protection law will be take into account. It is ensured that access to the data is strictly limited only to authorized persons who are involved in the sub-studies. Data are protected against unauthorized access.
15 ADMINISTRATIVE AGREEMENTS

15.1 Adherence to the Protocol

The clinical trial will be conducted in accordance with local laws and ICH guidelines for Good Clinical Practice (GCP) issued in June 1996 and CPMP/ICH/135/95 from September 1997, taking into account the Declaration of Helsinki and all its revisions. Protocol violations are any deviations from the procedures outlined in this document:

- missed evaluations/ incorrect timing of evaluations
- non-compliance with study medications/ intake of prohibited medications

After a patient has been enrolled, it is the investigator's responsibility to make a reasonable effort to correct any protocol violation in order to keep the subject in the study. Major protocol violations will be reported immediately to the scientific coordinator during the course of the study. The nature of these violations will be defined in the monitoring manual. All protocol violations will be listed and discussed with the scientific coordinator and biometrician prior to statistical analysis.

The investigator makes every effort to conduct the study according to the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the investigator. All such deviations will be documented in the records, together with the reason for their occurrence, and where appropriate, detailed in the study report.

15.2 Protocol Amendments

In order to ensure most comparable conditions during all sessions of the trial and in the interests of valid statistical analysis, the investigators, the coordinating investigator or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases and by mutual agreement within the steering committee. Any amendment must be set out in writing, at the same time giving the reasons, and signed by all parties concerned. The amendment then becomes part of the study protocol, and is to be filed in the Trial Master File (TMF).

Amendments which might have an impact on the well-being of the subject (major amendments) such as the use of additional invasive diagnostic procedures require an additional approval by the Ethics Committee (EC) and by the competent federal authority (BfArM). In addition, a further
informed consent form is to be signed by all trial subjects enrolled in the trial that might be affected by the amendment. Minor changes will only be submitted to the Ethics Committee and the competent federal authority in a written form (for further details see section 12.3). The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval opinion. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted to the coordinating investigator for agreement.

15.3 Funding

HYPRESS is funded by Supported by the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF), Project-Code: 01 KG 07 01.

15.4 Insurance

Patients are insured by the insurance company GERLING Vertrieb Deutschland GmbH, Regionalzentrum West, Abteilung H/RS Industrie, Prinzenallee 21, 40549 Düsseldorf. The number of the insurance police is: 70-5644584-4. The maximum insurance sum per patient is 500.00,00 €. A copy of the insurance policy and the insurance conditions will be filed in the investigator site file and a copy handed out to the patients.

15.5 Notification to Local Authorities

Prior to enrolment of the first patients into the trial the sponsor and all investigators are responsible for notification of his/her participation in the trial to the local regulatory authority, according to the German drug law (AMG §67 and the requirements of the GCP-V §12) [ARZNEIMITTELGESETZ - AMG 2004,GCP-VERORDNUNG - (GCP-V) 2004].

According to §67 AMG and §§ 12,13 GCP-V the sponsor and all investigators are also responsible to notify amendments, premature terminations of trial arms or of the whole study and the regular trial finish of the trial to the local regulatory authority [ARZNEIMITTELGESETZ - AMG 2004,GCP-VERORDNUNG - (GCP-V) 2004].

15.6 Publication Policy

It is planned that results of the HYPRESS study are published in peer reviewed international journals. The right for authorship is adapted to the recommendations of the Uniform
Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (www.icmje.org):

Authorship credit should be based on all three of the following conditions:

- Substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data.
- Drafting the article or revising it critically for important intellectual content.
- Final approval of the version to be published.

All participating centers and responsible investigators will be acknowledged in the publication. It is the right of participating centers to use the data for scientific purposes. After acknowledgement of the SepNet steering committee, scientific manuscripts may be published in the name of participating investigators.

HYPRESS will be registered at a central study register (e.g. www.clinicaltrials.gov)

15.7 Case Payment

Investigators will be reimbursed only for study-specific expenditures. The principal investigator delivers the account information to the Charité study team. The case payment will be transferred after completion of the eCRF including queries. Payments will be performed in batches every 4-6 months.
16 REFERENCES


17 CONFIRMATION OF THE FINAL PROTOCOL

The signatories declare that they agree to conduct their responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented.

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Datum (dd/mm/yyyy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coordinating Investigator</td>
<td>(Prof. Dr. K. Reinhart)</td>
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<tr>
<td>Administrative Coordinator</td>
<td>(Dr. F. Brunkhorst)</td>
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<tr>
<td>Scientific coordinator</td>
<td>(PD Dr. D. Keh)</td>
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<tr>
<td>Biometrician</td>
<td>(Dr. C. Engel)</td>
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</tbody>
</table>
18 PROTOCOL AGREEMENT

The signatory declares

- that he/she agrees to conduct his/her responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented
- that he/she has acquainted his/herself with the results of the pharmacological and toxicological trials of the investigational product and the results of other studies carried out to date
- that he/she has read the study protocol and agrees to it in its entirety
- that he/she intends to adhere to the schedule as specified below.

Date: _________________________

Signature of the principal investigator: _________________________

Affiliation /address: ________________________________________
                  ________________________________________
                  ________________________________________
19 APPENDIX

19.1 Definitions

19.1.1 Septic Shock

Septic shock is the primary endpoint in HYPRESS. Thus, the definition of septic shock is critical for conducting the study.

Septic shock is defined as a sepsis-induced hypotension despite adequate volume replacement with the following criteria:

- Mean arterial pressure (MAP) < 65 mmHg or systolic arterial pressure (SAP) < 90 mmHg OR the use of vasopressors to keep MAP ≥ 65 mmHg or SAP ≥ 90 mmHg, IF any of these conditions persist for 4 hours or more.
- Patients who received vasopressors only for limited time (e.g. initial volume resuscitation, anesthesia) are considered to be not in septic shock if they are free of vasopressors and have no hypotension for at least 2 hours before inclusion. Only norepinephrine is used as a vasopressor in HYPRESS.

In HYPRESS, only norepinephrine has to be used as a vasopressor, there is no indication for the use of dopamine, epinephrine or other vasopressors in the first line of treatment in patients with severe sepsis.

Adequate volume replacement is defined as:

Central venous pressure (CVP) ≥ 8 mmHg (≥ 12 mmHg during mechanical ventilation)

AND a

Central venous oxygen saturation (ScvO2) ≥ 70 %.

Vasopressors are defined as ≥ 5 μg/kg/min dopamine or any dose of epinephrine, norepinephrine, vasopressin, or other vasopressor.

It is recognized that there is no perfect definition of adequate volume status in critically ill patients established. The goals in HYPRESS are adapted to recommendations of the German Sepsis Society (GSS).

It is very important that patients receive adequate volume replacement by the use of crystalloids or colloids before vasopressors are initiated. The use of HES 200/0.5 is discouraged due to
increased risk of renal failure in patients with severe sepsis. Until additional data are available, the use of other HES preparations is not recommended in severe sepsis. According to GSS S2-guidelines, patients should receive at least 500-1000 ml of crystalloids or 300-500 ml of colloids over 30 min. The amount of fluids may be in the range of several liters in individual patients. Fluid administration should be guided by arterial pressure, CVP, and ScvO2. The rate of fluid administration should be reduced substantially when cardiac filling pressures (central venous pressure or balloon-occluded pressure) increase without concurrent hemodynamic improvement.

Patients who need vasopressors for treatment of episodes of hypotension should not be regarded to be in septic shock in the following situations:

- If vasopressors are used to bridge the time until adequate volume loading, e.g. during the early phase of severe sepsis and EGDT.
- If vasopressors are used only in small amounts for a limited time or sporadically e.g. during positioning, transport, CT-diagnostic, intubation etc.
- If it is obvious that hypotension is due to the use of hypotensive drugs (e.g. volatile anaesthetics) or fluid loss during anesthesia and surgery, and that it can be expected that the patient will be free of vasopressors after surgery.
- If continuous infusion of vasopressors is < 4 hours.

19.1.2 Study Day
In general, a study day begins at 6:00 and ends at 6:00 on the following day (= 24 hours).

The first study day (day 1) is defined as follows:
If the inclusion time is before 18:00 the first study day begins at the time of inclusion and ends on the next day at 6:00, i.e. the first study day is < 24 hours. The second day starts at 6:00.
If the inclusion time is after 18:00, the first study day begins at the time of inclusion and ends on the day after the next day at 6:00, i.e. the first study day is > 24 hours. The second day starts at 6:00.

Inclusion time is defined as the time of randomisation
### 19.2 Scores

**19.2.1 APACHE II (Acute Physiology and Chronic Health Evaluation)**

[KNAUS 1985]

#### THE APACHE II SEVERITY OF DISEASE CLASSIFICATION SYSTEM

<table>
<thead>
<tr>
<th>PHYSIOLOGIC VARIABLE</th>
<th>HIGH ABNORMAL RANGE</th>
<th>LOW ABNORMAL RANGE</th>
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</thead>
<tbody>
<tr>
<td><strong>TEMPERATURE</strong> (rectal °C)</td>
<td>32.4°C-38.5°C</td>
<td>≥38.5°C</td>
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<tr>
<td><strong>MEAN ARTERIAL PRESSURE</strong> (mm Hg)</td>
<td>65-70</td>
<td>&lt;65</td>
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<td><strong>HEART RATE</strong> (ventricular response)</td>
<td>20-30</td>
<td>≥30</td>
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<tr>
<td><strong>RESPIRATORY RATE</strong> (non-ventilated or ventilated)</td>
<td>10-20</td>
<td>≥20</td>
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<tr>
<td><strong>OXYGENATION</strong> (AaDo2 or PaO2, mm Hg)</td>
<td>100-200</td>
<td>&lt;100</td>
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<tr>
<td><strong>SERUM SODIUM</strong> (mmol/L)</td>
<td>135-150</td>
<td>&lt;135</td>
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<tr>
<td><strong>SERUM POTASSIUM</strong> (mmol/L)</td>
<td>4.5-5.5</td>
<td>&lt;4.5</td>
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<tr>
<td><strong>SERUM CREATININE</strong> (mg/dL)</td>
<td>1.1-1.9</td>
<td>&lt;1.1</td>
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<td><strong>HEMATOCRIT</strong> (%)</td>
<td>30-40</td>
<td>&lt;30</td>
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<tr>
<td><strong>WHITE BLOOD COUNT</strong> (total/mm³)</td>
<td>4.0-10.0</td>
<td>&lt;4.0</td>
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</table>

#### AGE POINTS:

- Assign points to age as follows:
  - <40: 0
  - 40-54: 1
  - 55-74: 2
  - ≥75: 3

#### CHRONIC HEALTH POINTS:

- Assign points to health status:
  - 0: No chronic health condition
  - 1: Long-term non-life-threatening condition
  - 2: Long-term life-threatening condition
  - 3: Requires medical care

#### CARDIOVASCULAR:

- New York Heart Association Class IV

#### RESPIRATORY:

- Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction, i.e., unable to climb stairs or perform household duties.

#### RENAL:

- Incarcerated chronic dialysis

#### IMMUNOCOMPROMISED:

- The patient has received therapy that suppresses resistance to infection, e.g., immunosuppression, chemotherapy, radiation, long-term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS.

#### APACHE II SCORE:

- Sum of APS points

#### GSOS:

- Score = 15 minus unique GCS

#### Total APACHE II:

- Sum of APS points and GSOS

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Page 98 of 133
### 19.2.2 SAPS 2 (Simplified Acute Physiology Score 2)

**[LE GALL 1993a; LE GALL 1993b]**

**Table 3—SAPS II Scoring Sheet**

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<thead>
<tr>
<th>Variable</th>
<th>Points:</th>
<th>25</th>
<th>13</th>
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<td>&lt;40</td>
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<td>Heart rate, beats/min</td>
<td>&lt;40</td>
<td>40-69</td>
<td>70-119</td>
<td>100-199</td>
<td>&lt;39</td>
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<td>Systolic BP, mm Hg</td>
<td>&lt;70</td>
<td>70-99</td>
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<td>Only if ventilated or continuous positive airway pressure</td>
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<td>PaO₂, mm Hg/FIO₂</td>
<td>&lt;13.3</td>
<td>13.3-26.5</td>
<td>≥26.6</td>
<td>0.500-0.999</td>
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<td>Urinary output, L/d</td>
<td>&lt;0.500</td>
<td>13.3-26.5</td>
<td>≥26.6</td>
<td>0.500-0.999</td>
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<td>Serum urea level, mmol/L or serum urea nitrogen level, mg/dL</td>
<td>&lt;10.0</td>
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<td>WBC count (10⁹/μL mm)</td>
<td>&lt;1.0</td>
<td>1.0-19.9</td>
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<td>Serum potassium, mmol/d</td>
<td>&lt;3.0</td>
<td>3.0-4.9</td>
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<td>Serum sodium level, mmol/L</td>
<td>&lt;125</td>
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<td>Serum bicarbonate level, mEq/L</td>
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<td>Bilirubin level, μmol/L (mg/dL)</td>
<td>&lt;68.4</td>
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<td>Glasgow Coma Score</td>
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*SAPS indicates Simplified Acute Physiology Score; BP blood pressure; FIO₂ fraction of inspired oxygen; kPa, kilopascal; WBC, white blood cell; and AIDS, acquired immunodeficiency syndrome.*
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<td>Age</td>
<td>Use the patient's age (in years) at last birthday</td>
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<td>Heart rate</td>
<td>Use the worst value in 24 hours, either low or high heart rate; if it varied from cardiac arrest (11 points) to extreme tachycardia (7 points), assign 11 points</td>
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<td>Systolic blood pressure</td>
<td>Use the same method as for heart rate; eg, if it varied from 80 mm Hg to 205 mm Hg, assign 13 points</td>
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<td>Body temperature</td>
<td>Use the highest temperature in degrees Centigrade or Fahrenheit</td>
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<td>(\text{Pao}_2/\text{FiO}_2) ratio</td>
<td>If ventilated or continuous positive airway pressure use the lowest value of the ratio</td>
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<td>Urinary output</td>
<td>If the patient is in the intensive care unit for less than 24 hours, make the calculation for 24 hours: eg, 1 L in 8 hours = 3 L in 24 hours</td>
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<td>Serum urea or serum urea nitrogen level</td>
<td>Use the highest value in mmol/L or g/L for serum urea, in mg/dL, for serum urea nitrogen</td>
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<td>WBC count</td>
<td>Use the worst (high or low) WBC count according to the scoring sheet</td>
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<td>Serum potassium level</td>
<td>Use the worst (high or low) value in mmol/L, according to the scoring sheet</td>
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<td>Serum sodium level</td>
<td>Use the worst (high or low) value in mmol/L, according to the scoring sheet</td>
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<td>Serum bicarbonate level</td>
<td>Use the lowest value in mEq/L</td>
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<td>Bilirubin level</td>
<td>Use the highest value in (\mu)mol/L or mg/dL</td>
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<td>Glasgow Coma Score</td>
<td>Use the lowest value; if the patient is sedated, record the estimated Glasgow Coma Score before sedation</td>
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<td>Type of admission</td>
<td>Unscheduled surgical, (\dagger) scheduled surgical, (\ddagger) medical</td>
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<td>AIDS</td>
<td>Yes, if HIV-positive with clinical complications such as Pneumocystis carinii pneumonia, Kaposi's sarcoma, lymphoma, tuberculosis, or toxoplasma infection</td>
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<td>Hematologic malignancy</td>
<td>Yes, if lymphoma, acute leukemia, or multiple myeloma</td>
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<td>Metastatic cancer</td>
<td>Yes, if proven metastasis by surgery, computed tomographic scan, or any other method</td>
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*SAPS* indicates Simplified Acute Physiology Score; \(\text{FiO}_2\), fraction of inspired oxygen; WBC, white blood cell; AIDS, acquired immunodeficiency syndrome; and HIV, human immunodeficiency virus.

\(\dagger\)Patients added to operating room schedule within 24 hours of the operation.

\(\ddagger\)Patient whose surgery was scheduled at least 24 hours in advance.

\(\dagger\)Patients having no surgery within 1 week of admission to intensive care unit.
### 19.2.3 SAPS 3 (Simplified Acute Physiology Score 3)

[METNITZ 2005, MORENO 2005]

#### Table 1 SARS 3 admission scoresheet—Part 1

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<td>Co-Morbidities</td>
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<td>41-50</td>
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<td>Length of stay before ICU admission, days</td>
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<td>Intensive care before ICU admission</td>
<td>Emergency room</td>
<td>Other ICU</td>
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<td>Use of major therapeutic options before ICU admission</td>
<td>Vasopressor drugs</td>
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<td>&lt;2</td>
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<td>Heart rate (highest), beats/minute</td>
<td>&lt;120</td>
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<td>PaO2/FiO2 &lt;300</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and MV</td>
<td>MV</td>
<td>MV</td>
<td>MV</td>
<td>MV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>and MV</td>
<td>MV</td>
<td>MV</td>
<td>MV</td>
<td>MV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2 SAPS 3 admission scoresheet – Part 2

<table>
<thead>
<tr>
<th>ICU admission</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason(s) for ICU admission</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular: Rhythm disturbances</td>
<td>-5</td>
</tr>
<tr>
<td>Neurologic: Seizures</td>
<td>-4</td>
</tr>
<tr>
<td>Cardiovascular: Hypovolemic hemorrhagic shock</td>
<td>3</td>
</tr>
<tr>
<td>Hypovolemic non hemorrhagic shock</td>
<td>3</td>
</tr>
<tr>
<td>Digestive: Acute abdomen, Other</td>
<td>1</td>
</tr>
<tr>
<td>Neurologic: Coma, Sepsis, Obtunded patient</td>
<td>4</td>
</tr>
<tr>
<td>Vigilance disturbances, Confusion, Agitation, Delirium</td>
<td>4</td>
</tr>
<tr>
<td>Cardiovascular: Septic shock, Cardiovascular:</td>
<td>5</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>5</td>
</tr>
<tr>
<td>Hemiplegic: Liver failure</td>
<td>6</td>
</tr>
<tr>
<td>Neurologic: Focal neurologic deficit</td>
<td>7</td>
</tr>
<tr>
<td>Digestive: Severe pancreatitis</td>
<td>9</td>
</tr>
<tr>
<td>Neurologic: Intracranial mass effect</td>
<td>10</td>
</tr>
<tr>
<td>All others</td>
<td>0</td>
</tr>
<tr>
<td>Anatomical site of surgery</td>
<td></td>
</tr>
<tr>
<td>Transplantation surgery: Liver, Kidney, Pancreas,</td>
<td>-11</td>
</tr>
<tr>
<td>Kidney and pancreas, Transplantation other</td>
<td>-11</td>
</tr>
<tr>
<td>Trauma – Other, Isolated</td>
<td>-8</td>
</tr>
<tr>
<td>(includes Thorax, Abdomen, limb); Trauma – Multiple</td>
<td>-8</td>
</tr>
<tr>
<td>Cardiac surgery: CABG without valvular repair</td>
<td>-6</td>
</tr>
<tr>
<td>Neurosurgery: Cerebrovascular accident</td>
<td>5</td>
</tr>
<tr>
<td>All others</td>
<td>0</td>
</tr>
</tbody>
</table>

12) Every patient gets an offset of 16 points for being admitted (to avoid negative SAPS 3 Scores).
13) If both reasons for admission are present, only the worse value (-4) is scored.
### 19.2.4 SOFA (Sepsis-related Organ Failure Assessment)

[VINCENT 1996]

<table>
<thead>
<tr>
<th>Organ System</th>
<th>SOFA points</th>
<th>NOTE:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td>Use worst values within 24 hours. Use highest cathecholamine dosage for at least 1 hour within 24 hours.</td>
</tr>
<tr>
<td>PaO₂/FiO₂</td>
<td>≥ 400</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>&lt; 400</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt; 300</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt; 200</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt; 100</td>
<td>4</td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td>If blood gas analysis is not available, estimate PaO₂ from arterial oxygen saturation (pulsoximetry) (see 19.2.6)</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥ 150</td>
<td>0</td>
</tr>
<tr>
<td>X 10³/µl</td>
<td>&lt; 150</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>&lt; 100</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&lt; 50</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&lt; 20</td>
<td>4</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
<td>In non-ventilated patients, estimate FiO₂ from conversion table (see 19.2.6)</td>
</tr>
<tr>
<td>GCS</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Glasgow Coma Scale</td>
<td>13-14</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>10-12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6-9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>3-5</td>
<td>4</td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td>For GCS see 19.2.5</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt; 1.2</td>
<td>0</td>
</tr>
<tr>
<td>mg/dl</td>
<td>1.2-1.9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2.0-5.9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>6.0-11.9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥ 12</td>
<td>4</td>
</tr>
<tr>
<td><strong>Kidney</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output (mg/dl)</td>
<td>&lt; 1.2</td>
<td>0</td>
</tr>
<tr>
<td>(ml/day)</td>
<td>1.2-1.9</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>2.0-3.4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3.5-4.9</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>200-499</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>&gt; 5.0</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&lt; 200</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>MAP ≥ 70</td>
<td>0</td>
</tr>
<tr>
<td>Mean arterial pressure</td>
<td>MAP &lt; 70</td>
<td>1</td>
</tr>
<tr>
<td>Catecholamines in µg/kg/min</td>
<td>Any Dobutamine</td>
<td>2</td>
</tr>
<tr>
<td>VP: Vasopressor</td>
<td>DOP ≤ 5</td>
<td>2</td>
</tr>
<tr>
<td>NE: Norepinephrine</td>
<td>DOP &gt; 15</td>
<td>4</td>
</tr>
<tr>
<td>DOP: Dopamine</td>
<td>EPI or NE ≤ 0.1</td>
<td>3</td>
</tr>
<tr>
<td>EPI: Epinephrine</td>
<td>EPI or NE &gt; 0.1</td>
<td>4</td>
</tr>
</tbody>
</table>
### 19.2.5 GCS (Glasgow Coma Scale)

[TEASDALE 1974]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye Opening Response</strong></td>
<td></td>
</tr>
<tr>
<td>Spontaneous – open with blinking at baseline</td>
<td>4</td>
</tr>
<tr>
<td>Opens to verbal command, speech, or shout</td>
<td>3</td>
</tr>
<tr>
<td>Open to pain, not applied to face</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td><strong>Verbal Response</strong></td>
<td></td>
</tr>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused conversation, but able to answer questions</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate response, words discernible</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible speech</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td><strong>Motor Response</strong></td>
<td></td>
</tr>
<tr>
<td>Obeys commands for movement</td>
<td>6</td>
</tr>
<tr>
<td>Purposeful movement to painful stimulus</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal from pain</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal (spastic) flexion, decorticate posture</td>
<td>3</td>
</tr>
<tr>
<td>Extensor (rigid) response, decerebrate posture</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

**NOTE:**
- If GCS can be evaluated in a non-sedated patient, the lowest score during non-sedation is documented.
- If evaluation of GCS is based on values during non-sedation and sedation, the lowest non-sedated value is documented.
- If the patient is sedated, the lowest value before sedation is documented.
- In general, in sedated patients values are estimated from the status before sedation was initiated.
- In the CRF, it is documented whether values have been evaluated or estimated.
### 19.2.6 Conversion Table $\text{SaO}_2 / \text{PaO}_2$

<table>
<thead>
<tr>
<th>$\text{SO}_2$ (%)</th>
<th>Estimated $\text{PaO}_2$ (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>81</td>
<td>45</td>
</tr>
<tr>
<td>82</td>
<td>46</td>
</tr>
<tr>
<td>83</td>
<td>47</td>
</tr>
<tr>
<td>84</td>
<td>49</td>
</tr>
<tr>
<td>85</td>
<td>50</td>
</tr>
<tr>
<td>86</td>
<td>52</td>
</tr>
<tr>
<td>87</td>
<td>53</td>
</tr>
<tr>
<td>88</td>
<td>55</td>
</tr>
<tr>
<td>89</td>
<td>57</td>
</tr>
<tr>
<td>90</td>
<td>60</td>
</tr>
<tr>
<td>91</td>
<td>62</td>
</tr>
<tr>
<td>92</td>
<td>65</td>
</tr>
<tr>
<td>93</td>
<td>69</td>
</tr>
<tr>
<td>94</td>
<td>73</td>
</tr>
<tr>
<td>95</td>
<td>79</td>
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<tr>
<td>96</td>
<td>86</td>
</tr>
<tr>
<td>97</td>
<td>96</td>
</tr>
<tr>
<td>98</td>
<td>112</td>
</tr>
<tr>
<td>99</td>
<td>145</td>
</tr>
</tbody>
</table>

### 19.2.7 Estimated $\text{FiO}_2$ during oxygen insufflation

<table>
<thead>
<tr>
<th>Method</th>
<th>$\text{O}_2$-Flow (L/min)</th>
<th>Estimated $\text{FiO}_2$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Canula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>44</td>
<td></td>
</tr>
<tr>
<td>Nasopharyngeal Canula</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Face Mask</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>6-7</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>7-8</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>Face Mask + Reservoir</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>95</td>
<td></td>
</tr>
</tbody>
</table>
19.2.8 MRC Scale (Medical Research Council Scale)

The MRC scale evaluates the muscle strength of three muscle groups in each of the upper and lower limbs. Each muscle group score ranges from 0 (paralysis) to 5 (normal muscle strength), and the overall score from 0 to 60. Patients with a MRC score less than 48 are considered to have a clinically significant muscle weakness [DE JONGHE 2004b].

The MRC is performed in eligible patients until day 28 or ICU discharge, whatever comes first. Before the MRC can be assessed, patients have to be screened for awakening and comprehension based on their response to 5 questions. At least three of them have to be responded adequately:

- “Open (close) your eyes”
- “Look at me”
- “Open your mouth and put out your tongue”
- “Nod your head”
- “Raise your eyebrows when I have counted up to 5”

<table>
<thead>
<tr>
<th>Medical research council neuromuscular scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Movements tested (6 on each side)</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Arm abduction</td>
</tr>
<tr>
<td>Elbow flexion</td>
</tr>
<tr>
<td>Wrist extension</td>
</tr>
<tr>
<td>Hip flexion</td>
</tr>
<tr>
<td>Knee extension</td>
</tr>
<tr>
<td>Ankle dorsiflexion</td>
</tr>
</tbody>
</table>

Each limb is assigned a score from 0 to 15. Therefore, the total score can range from 0 (complete tetraplegia) to 60 (normal muscle strength).

The CRF contains for every limb a score for movement to be inserted. The score will be calculated from row data.

**NOTE:** If a limb can not be scored due to injury (e.g. fixateur externe), the score of the contra-lateral limb is calculated for both sides. If both sides can not be scored due to injury, muscle strength is calculated from not injured limbs. It is documented in the CRF that examination cannot be performed due to injury etc.. Calculations will be performed during data analysis.

If the MRC scale can not be performed (e.g. sedation), state ‘not applicable’.
19.3 CAM-ICU (Confusion Assessment Method for ICU) and RASS (Richmond Agitation and Sedation Scale)


**Stufe 1: Erfassen der Sedierung**

Die „Richmond Agitation and Sedation Scale“: RASS *

<table>
<thead>
<tr>
<th>Score</th>
<th>Bezeichnung</th>
<th>Beschreibung</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>sehr streitsüchtig</td>
<td>gewalttätig, unmittelbare Gefahr für das Personal</td>
</tr>
<tr>
<td>+3</td>
<td>sehr agitiert</td>
<td>Aggressiv, zieht Drainagen und Katheter heraus</td>
</tr>
<tr>
<td>+2</td>
<td>agitiert</td>
<td>häufige ungezielte Bewegungen, kämpft gegen das Beatmungsgerät</td>
</tr>
<tr>
<td>+1</td>
<td>unruhig</td>
<td>ängstlich, aber Bewegungen nicht aggressiv oder heftig</td>
</tr>
<tr>
<td>0</td>
<td>aufmerksam, ruhig</td>
<td>nicht ganz aufmerksam, aber erweckbar auf Ansprache (Augenöffnen und Augenkontakt ≥ 10 sec)</td>
</tr>
<tr>
<td>−1</td>
<td>schlaftrunken</td>
<td>kurzes Erwachen, Augenkontakt auf Ansprache &lt; 10 sec.</td>
</tr>
<tr>
<td>−2</td>
<td>leichte Sedierung</td>
<td>Bewegung oder Augenöffnen auf Ansprache, aber kein Augenkontakt</td>
</tr>
<tr>
<td>−3</td>
<td>mäßige Sedierung</td>
<td>Keine Reaktion auf Ansprache, aber Bewegung oder Augenöffnen durch Berührung</td>
</tr>
<tr>
<td>−4</td>
<td>tiefe Sedierung</td>
<td>Keine Reaktion auf Ansprache oder Berührung</td>
</tr>
<tr>
<td>−5</td>
<td>nicht erweckbar</td>
<td>Keine Reaktion auf Ansprache oder Berührung</td>
</tr>
</tbody>
</table>

falls RASS −4 oder −5 → STOP, spätere Wiederholung
falls RASS über −4 (−3 bis +4) → weiter zu Stufe 2

**Stufe 2: Delir-Einstufung**

**Merkmal 1:** akute Veränderung des geistigen Zustandes oder fluktuiender Verlauf

UND

**Merkmal 2:** Aufmerksamkeitsstörung

UND

**Merkmal 3:** Unorganisiertes Denken

ODER

**Merkmal 4:** Bewußtseinsstörung

= DELIR
Confusion Assessment Method für Intensivstation CAM-ICU

RASS ist -3 bis +4? 
weiter zur nächsten Stufe

Hinweis: RASS -3 oft nicht unterschätzbar, später erneut untersuchen. 
RASS +3 / +4 oft nicht kooperativ, CAM-ICU positiv.

RASS ist -4 oder 5? 
STOP 
Pat. später erneut untersuchen

Richmond-Scale (RASS)

1. Psychische Veränderungen? 
Aktiver Regen? (z.B. zu früh beim Stohlen?) 
Ändert sich das Verhalten im Tagesverlauf?

NEIN 
STOP 
Kein Delir

JA

2. Aufmerksamkeitsstörung
Lesen Sie dem Pat. folgende Buchstaben vor: A N A S B A U M
Fehler: Pat. erkennt beim 'A' nicht die Hand
Fehler: Pat. drückt bei einer anderen Buchstaben als 'A'

1 oder 2 Fehler
STOP 
Kein Delir

3. Fehler oder mehr

3. Bewusstseinsveränderung ("aktuelles" RASS)
Falls RASS = 0 weiter zur nächsten Stufe
Falls RASS < 0 ist
Delir

4. unorganisiertes Denken
1. Schwimmt ein Stein auf dem Wasser? (Schwimmt ein Bart auf dem Wasser?)
2. Ist die Physik im Moos? (Oben und Unten gleich weit entfernt?)
3. Wieviele Kilo mehr als zwei Kilo? (Wie viele Kilo mehr als zwei Kilo?)
4. Kann man mit einem Hammer einen Nagel in die Wand schlagen? (Kann man mit einem Hammer Holz schlagen?)
5. Anweisung: 
Sagen Sie dem Pat.: "Halten Sie zwei Finger hoch." (Unterlassen Sie drei Finger hoch)
"Nehmen Sie die andere Hand;" (Wiederholen Sie nicht drei Finger hoch)
Falls Pat. nicht beide Hände bewegen kann: "Fugen Sie einen Finger anzuzeig.

2 oder mehr Fehler 
Delir

< 2 Fehler 
STOP 
Kein Delir
19.4 Posttraumatic Stress Disorder (PTSD) and Health-related Quality of Life (HrQoL)

19.4.1 Quality Adjusted Life Years (EuroQol)

**EuroQol**

Bitte geben Sie an, welche Aussagen Ihren heutigen Gesundheitszustand am besten beschreiben, indem Sie ein Kreuz (x) in ein Kästchen jeder Gruppe machen.

1. **Beweglichkeit / Mobilität**
   - Ich habe keine Probleme herumzugehen. □
   - Ich habe einige Probleme herumzugehen. □
   - Ich bin ans Bett gebunden. □

2. **Für sich selbst sorgen**
   - Ich habe keine Probleme, für mich selbst zu sorgen. □
   - Ich habe einige Probleme, mich selbst zu waschen oder mich anzuziehen. □
   - Ich bin nicht in der Lage, mich selbst zu waschen oder anzuziehen. □

3. **Allgemeine Tätigkeiten (z.B. Arbeit, Studium, Hausarbeit, Familien- oder Freizeitaktivitäten)**
   - Ich habe keine Probleme, meinen alltäglichen Tätigkeiten nachzugehen. □
   - Ich habe einige Probleme, meinen alltäglichen Tätigkeiten nachzugehen. □
   - Ich bin nicht in der Lage, meinen alltäglichen Tätigkeiten nachzugehen. □

4. **Schmerzen / Körperliche Beschwerden**
   - Ich habe keine Schmerzen oder Beschwerden. □
   - Ich habe mäßige Schmerzen oder Beschwerden. □
   - Ich habe extreme Schmerzen oder Beschwerden. □

5. **Angst / Niedergeschlagenheit**
   - Ich bin nicht ängstlich oder deprimiert. □
   - Ich bin mäßig ängstlich oder deprimiert. □
   - Ich bin extrem ängstlich oder deprimiert. □
6. Verglichen mit meinem allgemeinen Gesundheitszustand während der vergangenen 12 Monate ist mein heutiger Gesundheitszustand
besser
im großen und ganzen etwa gleich
schlechter

7. Um Sie bei der Einschätzung, wie gut oder wie schlecht Ihr Gesundheitszustand ist, zu unterstützen, haben wir eine Skala gezeichnet, ähnlich einem Thermometer. Der best denkbarer Gesundheitszustand ist mit „100“ gekennzeichnet, der schlechteste mit „0“.

Wir möchten Sie nun bitten, auf dieser Skala zu kennezeichnen, wie gut oder schlecht Ihrer Ansicht nach Ihr persönlicher Gesundheitszustand heute ist. Bitte verbinden Sie dazu den untenstehenden Kasten mit dem Punkt auf der Skala, der Ihren heutigen Gesundheitszustand am besten wiedergibt.
19.4.2 Medical Outcomes Study Short Form Survey (SF-36)

Patienten-Fragebogen zum Gesundheitszustand*

* SF-36 Health Survey, Copyright© 1992 Medical Outcomes Trust

In diesem Fragebogen geht es um Ihre Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht es, im Zeitverlauf nachzuverfolgen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte beantworten Sie jede der folgenden Fragen, indem Sie bei den Antwortmöglichkeiten die Zahl ankreuzen, die am besten auf Sie zutrifft.

1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?

(Bitte kreuzen Sie nur eine Zahl an)

<table>
<thead>
<tr>
<th>Ausgezeichnet</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sehr gut</td>
<td>2</td>
</tr>
<tr>
<td>Gut</td>
<td>3</td>
</tr>
<tr>
<td>Weniger gut</td>
<td>4</td>
</tr>
<tr>
<td>Schlecht</td>
<td>5</td>
</tr>
</tbody>
</table>

2. Im Vergleich zum vergangenen Jahr, wie würden Sie Ihren derzeitigen Gesundheitszustand beschreiben?

(Bitte kreuzen Sie nur eine Zahl an)

| Derzeit viel besser als vor einem Jahr | 1 |
| Derzeit etwas besser als vor einem Jahr | 2 |
| Etwa so wie vor einem Jahr              | 3 |
| Derzeit etwas schlechter als vor einem Jahr | 4 |
| Derzeit viel schlechter als vor einem Jahr | 5 |
3. Im Folgenden sind einige Tätigkeiten beschrieben, die Sie vielleicht an einem normalen Tag ausüben. **Sind Sie durch Ihren derzeitigen Gesundheitszustand bei diesen Tätigkeiten eingeschränkt?** Wenn ja, wie stark? (Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

<table>
<thead>
<tr>
<th>TÄTIGKEITEN</th>
<th>Ja, stark eingeschränkt</th>
<th>Ja, etwas eingeschränkt</th>
<th>Nein, über-haupt nicht eingeschränkt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) anstrengende Tätigkeiten, z.B. schnell laufen, schwere Gegenstände heben, anstrengenden Sport treiben</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>b) mittelschwere Tätigkeiten, z.B. einen Tisch verschieben, staubsaugen, kegeln, Golf, spielen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>c) Einkaufstaschen heben oder tragen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>d) mehrere Treppenabsätze steigen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e) einen Treppenabsatz steigen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>f) sich beugen, knien, bücken</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>g) mehr als 1 Kilometer zu Fuß gehen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>h) mehrere Straßenkreuzungen weit zu Fuß gehen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>i) eine Straßenkreuzung weit zu Fuß gehen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>j) sich baden oder anziehen</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

4. Hatten Sie in den **vergangenen vier Wochen aufgrund Ihrer körperlichen Gesundheit irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause?**

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

<table>
<thead>
<tr>
<th>SCHWIERIGKEITEN</th>
<th>Ja</th>
<th>Nein</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ich konnte nicht so lange wie üblich tätig sein</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>b) Ich habe weniger geschafft als ich wollte</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>c) Ich konnte nur bestimmte Dinge tun</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>d) Ich hatte Schwierigkeiten bei der Ausführung (z.B. ich mußte mich besonders anstrengen)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
5. Hatten Sie in den **vergangenen vier Wochen aufgrund seelischer Probleme** irgendwelche Schwierigkeiten bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten)?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

<table>
<thead>
<tr>
<th>SCHWIERIGKEITEN</th>
<th>Ja</th>
<th>Nein</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ich konnte nicht so lange wie üblich tätig sein</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>b) Ich habe weniger geschafft als ich wollte</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>c) Ich konnte nicht so sorgfältig wie üblich arbeiten</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

6. Wie sehr haben Ihre körperliche Gesundheit oder seelische Probleme in den **vergangenen vier Wochen** Ihre normalen Kontakte zu Familienangehörigen, Freunden, Nachbarn oder im Bekanntenkreis beeinträchtigt?

(Bitte kreuzen Sie nur eine Zahl an)

<table>
<thead>
<tr>
<th>Überhaupt nicht</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etwas</td>
<td>2</td>
</tr>
<tr>
<td>Mäßig</td>
<td>3</td>
</tr>
<tr>
<td>Ziemlich</td>
<td>4</td>
</tr>
<tr>
<td>Sehr</td>
<td>5</td>
</tr>
</tbody>
</table>

7. Wie stark waren Ihre Schmerzen in den **vergangenen vier Wochen**?

(Bitte kreuzen Sie nur eine Zahl an)

<table>
<thead>
<tr>
<th>Ich hatte keine Schmerzen</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sehr leicht</td>
<td>2</td>
</tr>
<tr>
<td>Leicht</td>
<td>3</td>
</tr>
<tr>
<td>Mäßig</td>
<td>4</td>
</tr>
<tr>
<td>Stark</td>
<td>5</td>
</tr>
<tr>
<td>Sehr stark</td>
<td>6</td>
</tr>
</tbody>
</table>
8. Inwieweit haben die Schmerzen Sie in den vergangenen vier Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?

(Bitte kreuzen Sie nur eine Zahl an)

<table>
<thead>
<tr>
<th>Schmerzen</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Überhaupt nicht</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ein bisschen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mäßig</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziemlich</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sehr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. In diesem Fragen geht es darum, wie Sie sich fühlen und wie es Ihnen in den vergangenen vier Wochen gegangen ist (bitte kreuzen Sie in jeder Zeile die Zahl an, die Ihrem Befinden am ehesten entspricht). Wie oft waren Sie in den vergangenen vier Wochen

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

<table>
<thead>
<tr>
<th>BEFINDEN</th>
<th>Immer</th>
<th>Meistens</th>
<th>Ziemlich oft</th>
<th>Manch-mal</th>
<th>Selten</th>
<th>Nie</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) ... voller Schwung?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>b) ... sehr nervös?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>c) ... so niedergeschlagen, daß Sie nichts aufheitern könnte?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>d) ... ruhig und gelassen?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>e) ... voller Energie?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>f) ... entmutigt und traurig?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>g) ... erschöpft?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>h) ... glücklich</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>i) ... müde?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
10. Wie häufig haben Ihre körperliche Gesundheit oder seelischen Probleme in den 
vergangen vier Wochen Ihre Kontakte zu anderen Menschen (Besuche bei Freunden, 
Verwandten usw.) beeinträchtigt?

(Bitte kreuzen Sie nur eine Zahl an)

<table>
<thead>
<tr>
<th></th>
<th>Immer</th>
<th>Meistens</th>
<th>Manchmal</th>
<th>Selten</th>
<th>Nie</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

11. Inwieweit trifft jede der folgenden Aussagen auf Sie zu?

(Bitte kreuzen Sie in jeder Zeile nur eine Zahl an)

<table>
<thead>
<tr>
<th>AUSSAGEN</th>
<th>trifft ganz zu</th>
<th>trifft weitgehend zu</th>
<th>weiß nicht</th>
<th>trifft weitgehend nicht zu</th>
<th>trifft überhaupt nicht zu</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Ich scheine etwas leichter als andere krank zu werden</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>b) Ich bin genauso gesund wie alle anderen, die ich kenne</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>c) Ich erweise, daß meine Gesundheit nachläßt</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>d) Ich erfreue mich ausgezeichneter Gesundheit</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
19.4.3 Hospital Anxiety and Depression Scale (HADS-D)

![HADS-D Scale](image)

Sehr geehrte Patientin, sehr geehrter Patient!


Die Beantwortung ist selbstverständlich freiwillig. Wir bitten Sie jedoch, jede Frage zu beantworten, und zwar so, wie es für Sie persönlich in der letzten Woche am ehesten zutrifft. Machen Sie bitte nur ein Kreuz pro Frage und lassen Sie bitte keine Frage aus! Überlegen Sie bitte nicht lange, sondern wählen Sie die Antwort aus, die Ihnen auf Anhieb am zutreffendsten erscheint! Alle Ihre Antworten unterliegen der ärztlichen Schweigepflicht.

**HADS-D**

<table>
<thead>
<tr>
<th>Code-Nummer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Datum:</td>
</tr>
</tbody>
</table>

**Ich fühle mich angespannt oder überreizt**

- [ ] meistens
- [ ] oft
- [ ] von Zeit zu Zeit/gelegentlich
- [ ] überhaupt nicht

**Ich kann mich heute noch so freuen wie früher**

- [ ] ganz genau so
- [ ] nicht ganz so sehr
- [ ] nur noch ein wenig
- [ ] kaum oder gar nicht

**Mich überkommt eine ängstliche Vorahnung, dass etwas Schreckliches passieren könnte**

- [ ] ja, sehr stark
- [ ] ja, aber nicht allzu stark
- [ ] etwas, aber es macht mir keine Sorgen
- [ ] überhaupt nicht

**Ich kann lachen und die lustige Seite der Dinge sehen**

- [ ] ja, so viel wie immer
- [ ] nicht mehr ganz so viel
- [ ] inzwischen viel weniger
- [ ] überhaupt nicht

**Mir gehen banalierende Gedanken durch den Kopf**

- [ ] einen Großteil der Zeit
- [ ] verhältnismäßig oft
- [ ] von Zeit zu Zeit, aber nicht allzu oft
- [ ] nur gelegentlich/nie

**Ich fühle mich glücklich**

- [ ] überhaupt nicht
- [ ] selten
- [ ] manchmal
- [ ] meistens

**Ich kann behaglich dastehen und mich entspannen**

- [ ] ja, natürlich
- [ ] gewöhnlich schon
- [ ] nicht oft
- [ ] überhaupt nicht

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HUBER Bestellnummer 0306903
19.4.4 Posttraumatic Diagnostic Scale (PDS)

**Posttraumatic Diagnostic Scale (PDS)**
Foa 1995, dt. Übersetzung Ehlers, Steil & Winter

**Teil 1**

Viele Menschen haben irgendwann einmal in ihrem Leben ein sehr belastendes oder traumatisches Erlebnis oder wurden Zeugen eines solchen Ereignisses. Bitte geben Sie für jedes der folgenden Ereignisse an, ob Sie es erlebt haben, entweder persönlich oder als Zeuge. Bitte kreuzen Sie JA an, wenn dies der Fall war, und NEIN, wenn dies nicht der Fall war.

1. Schwerer Unfall, Feuer oder Explosion (z.B. Arbeitsunfall, Unfall in der Landwirtschaft, Autounfall, Flugzeug- oder Schiffsunglück)  
   JA NEIN

2. Naturkatastrophe (z.B. Wirbelsturm, Orkan, Flutkatastrophe, schweres Erdbeben)  
   JA NEIN

3. Gewalttätiger Angriff durch jemanden aus dem Familien- oder Bekanntenkreis (z.B. körperlich angegriffen, ausgeraubt, angeschossen oder mit einer Schusswaffe bedroht worden, Stichverletzung zugefügt bekommen)  
   JA NEIN

4. Gewalttätiger Angriff durch fremde Person (z.B. körperlich angegriffen, ausgeraubt, angeschossen oder mit einer Schusswaffe bedroht worden, Stichverletzung zugefügt bekommen)  
   JA NEIN

5. Sexueller Angriff durch jemanden aus dem Familien- oder Bekanntenkreis (z.B. Vergewaltigung oder versuchte Vergewaltigung)  
   JA NEIN

6. Sexueller Angriff durch eine fremde Person (z.B. Vergewaltigung oder versuchte Vergewaltigung)  
   JA NEIN

7. Kampfeinsatz im Krieg oder Aufenthalt in Kriegsgebiet  
   JA NEIN

8. Sexueller Kontakt im Alter von unter 18 Jahren mit einer Person, die mindestens 5 Jahre älter war (z.B. Kontakt mit Genitalien oder Brüsten)  
   JA NEIN

9. Gefangenschaft (z.B. Straf- oder Kriegsgefangenschaft, Geiselhaft)  
   JA NEIN

10. Folter  
    JA NEIN

11. Lebensbedrohliche Krankheit  
    JA NEIN

12. Anderes traumatisches Ereignis: bitte beschreiben Sie dieses:  

   ........................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................................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Teil 2

Wann hatten Sie dieses schlimmste Erlebnis?
(Bitte kreuzen Sie eine der Antwortmöglichkeiten an)

- Vor weniger als einem Monat
- Vor 1 bis 3 Monaten
- Vor 3 bis 6 Monaten
- Vor 6 Monaten bis 3 Jahren
- Vor drei bis 5 Jahren
- Vor mehr als 5 Jahren

Bitte kreuzen Sie für die folgenden Fragen JA oder NEIN an:
Während des schlimmsten Erlebnisses....

1. ... wurden Sie körperlich verletzt?  
2. ... wurde jemand anders körperlich verletzt?  
3. ... dachten Sie, daß Ihr Leben in Gefahr war?  
4. ... dachten Sie, daß das Leben einer anderen Person in Gefahr war?  
5. ... fühlten Sie sich hilflos?  
6. ... hatten Sie starke Angst oder waren Sie voller Entsetzen?

Teil 3

Im folgenden finden Sie eine Reihe von Problemen, die Menschen manchmal nach traumatischen Erlebnissen haben. Bitte lesen Sie sich jedes der Probleme sorgfältig durch. Wählen Sie diejenige Antwortmöglichkeit (0-3) aus, die am besten beschreibt, wie häufig Sie im letzten Monat (d.h. in den letzten vier Wochen bis einschließlich heute) von diesem Problem betroffen waren. Die Fragen sollten Sie dabei auf Ihr schlimmsten Erlebnis beziehen.

Dabei bedeutet:
0 = überhaupt nicht oder nur einmal im letzten Monat
1 = einmal pro Woche oder seltener, manchmal
2 = 2 bis 4 mal pro Woche, die Hälfte der Zeit
3 = 5 mal oder öfter pro Woche, fast immer.

1. Hatten Sie belastende Gedanken oder Erinnerungen an das Erlebnis, die ungewollt auftreten und Ihnen durch den Kopf gingen, obwohl Sie nicht daran denken wollten? 0 1 2 3

2. Hatten Sie schlechte Träume oder Alpträume über das Erlebnis? 0 1 2 3

3. War es, als würden Sie das Ereignis plötzlich noch einmal durchleben, oder handelten Sie so, als würde es wieder passieren? 0 1 2 3

4. Belastete es Sie, wenn Sie an das Erlebnis erinnert wurden (fühlten Sie sich z.B. ängstlich, ärgerlich, traurig, schuldig usw.)? 0 1 2 3

5. Hatten Sie körperliche Reaktionen (z.B. Schweissausbruch oder Herzklopfen), 0 1 2 3 als Sie an das Erlebnis erinnert wurden?
6. Haben Sie sich bemüht, nicht an das Erlebnis zu denken, nicht darüber zu reden oder damit verbundene Gefühle zu unterdrücken?

0 1 2 3

7. Haben Sie sich bemüht, Aktivitäten, Menschen oder Orte zu meiden, die Sie an das Erlebnis erinnern?

0 1 2 3

8. Konnten / können Sie sich an einen wichtigen Bestandteil des Erlebnisses nicht erinnern?

0 1 2 3

9. Hatten Sie deutlich weniger Interesse an Aktivitäten, die vor dem Erlebnis für Sie wichtig waren, oder haben Sie sie deutlich seltener unternommen?

0 1 2 3

10. Fühlten Sie sich Menschen Ihrer Umgebung gegenüber entfremdet oder isoliert?

0 1 2 3

11. Fühlten Sie sich abgestumpft oder taub (z.B. nicht weinen können oder sich unfähig fühlen, liebevolle Gefühle zu erleben)

0 1 2 3

12. Hatten Sie das Gefühl, daß sich Ihre Zukunftspläne und Hoffnungen nicht erfüllen werden (z.B. daß Sie im Beruf keinen Erfolg haben, nie heiraten, keine Kinder haben oder kein langes Leben haben werden)?

0 1 2 3

13. Hatten Sie Schwierigkeiten, ein- oder durchzuschlafen?

0 1 2 3

14. Waren Sie reizbar oder hatten Sie Wutanfälle?

0 1 2 3

15. Hatten Sie Schwierigkeiten, sich zu konzentrieren (z.B. während eines Gesprächs in Gedanken abschweifen, beim Ansehen einer Fernsehsendung den Faden verlieren; vergessen, was Sie gerade gelesen haben).

0 1 2 3

16. Waren Sie übermäßig wachsam (z.B. nachpräfen, wer in Ihrer Nähe ist, sich unwohl fühlen, wenn Sie mit dem Rücken zur Tür sitzen usw.)

0 1 2 3

17. Waren Sie nervös oder schreckhaft (z.B. wenn jemand hinter Ihnen geht).

0 1 2 3

Wie lange haben Sie schon die Probleme, die Sie in Teil 3 angegeben haben?
(Bitte eine Antwortmöglichkeit ankreuzen)

- weniger als einen Monat 0
- ein bis drei Monate 0
- über drei Monate 0

Wann nach dem traumatischen Erlebnis traten diese Probleme auf?
(Bitte eine Antwortmöglichkeit ankreuzen)

- innerhalb der ersten sechs Monate 0
- nach sechs Monaten oder später 0
**Teil 4**

Bitte geben Sie an, ob die Probleme, die Sie in Teil 3 angegeben haben, **im letzten Monat** in den unten aufgeführten Bereichen Ihres Lebens beeinträchtigt haben. Bitte kreuzen Sie JÄ an, wenn eine Beeinträchtigung vorlag, und NEIN, wenn dies nicht der Fall war.

<table>
<thead>
<tr>
<th>Bereich</th>
<th>JÄ</th>
<th>NEIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arbeit</td>
<td>JÄ</td>
<td>NEIN</td>
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<tr>
<td>Hausarbeit und Haushaltpflichten</td>
<td>JÄ</td>
<td>NEIN</td>
</tr>
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<td>Beziehungen zu Freunden</td>
<td>JÄ</td>
<td>NEIN</td>
</tr>
<tr>
<td>Unterhaltung und Freizeitaktivitäten</td>
<td>JÄ</td>
<td>NEIN</td>
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<td>(Hoch-) Schule oder Ausbildung</td>
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<td>NEIN</td>
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<td>Beziehungen zu Familienmitgliedern</td>
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<td>NEIN</td>
</tr>
<tr>
<td>Erotik</td>
<td>JÄ</td>
<td>NEIN</td>
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<tr>
<td>Allgemeine Lebenszufriedenheit</td>
<td>JÄ</td>
<td>NEIN</td>
</tr>
<tr>
<td>Allgemeine Leistungsfähigkeit in allen Lebensbereichen</td>
<td>JÄ</td>
<td>NEIN</td>
</tr>
</tbody>
</table>
19.4.5  Sociodemographical Data

Fragebogen zur Person I

Der folgende Fragebogen enthalt im ersten Teil einige Fragen zu Ihrer Person und im zweiten Teil Fragen zu Ihrem früheren sowie derzeitigen Gesundheitszustand. Bitte beantworten Sie alle Fragen durch Ankreuzen zutreffender Kästchen bzw. durch Ausfüllen markierter Bereiche.

Heutiges Datum: ________________
Geschlecht: maenlich          weiblich
Patient - ID: ________________

Ethnische Zugehoerigkeit: weiß          asiatisch          schwarz          andere: ________________

Familienstand: ledig          verheiratet/Partnerschaft
               geschieden          verwitwet

Wohnsituation: alleinlebend          mit Partner/ Familie

Schulabschluss: kein Abschluss
               Lehre/ Mittlere Reife
               Hochschulabschluss
               Volksschule/ Grundschule
               Matura/ Abitur

Derzeitiger beruflicher Status: vollzeit erwerbsfaehig
                                  teilzeit erwerbstaeatig
                                  arbeitslos
            im Haushalt taetig
            Altersrente/Pension
            erwerbsunfaehig [EU-Rente] auf
            Dauer seit ________________
            erwerbsunfaehig [EU-Rente] auf
            Zeit seit ________________
            geschuetzter Arbeitsplatz
            sonstiges: ________________

Falls erwerbstaelig: in Ausbildung/ Studium
                     Gelegenheitsarbeit

                     angestellt
                     selbststaendig,
                     freiberuflich
Fragen zum Gesundheitszustand II

1. Sind sie zur Zeit gehfähig?
   ja nein

2. Sind Sie fuer Ihre eigene Versorgung (Körperpflege, 
   Anziehen, Essen) auf fremde Hilfe angewiesen?
   ja nein

3. Hatten Sie im Erwachsenenalter andere schwerwiegende Erkrankungen? 
   Bitte Zutreffendes ankreuzen und bei jeder Erkrankung die genauen Angaben 
   machen:
   
3.1. Herzkrankungen (z.B.: Angina pectoris, Herzinfarkt, Herzschwäche,  
   Rhythmusstörungen) ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.2. Kreislauferkrankungen (z.B.: Hochdruck, Unterdruck, Schlaganfall,  
   Arterienverkalkung, Aneurysma) ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.3. Bösartige Erkrankungen / Tumoren ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.4. Erkrankungen des Nervensystems wie Anfallssyndrome (Epilepsie),  
   Nervenleiden, Gemütsstörungen ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.5. Stoffwechselerkrankungen (z.B.: Diabetes (Zucker), Gicht, Erhöhung der 
   Blutfettwerte, Schilddrüsen- und andere Hormonstörungen) ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.6. Lungenerkrankungen (z.B.: chronischer Husten, Asthma, Bronchitis, 
   Emphysem, Tuberkulose, Lungenentzündung) ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________

3.7. Magen-Darm- und Enddarmerkrankungen 
   (z.B.: Entzündungen, Geschwüre, Blutungen) ja nein
   Welche Erkrankung, in welchem Jahr, bzw. seit wann:____________________
3.8. **Harnwegserkrankungen** (Niere, Blase, Harnröhre):
   z. B.: Entzündungen, Steine, Blutungen, chronisches Nierenversagen  ja  nein

   Welche Erkrankung, in welchem Jahr, bzw. seit wann:__________________________

3.9. **Leber- und Bauchspeicheldrüsenerkrankung, Gallenleiden**
   (z. B.: Entzündungen, Steine)  ja  nein

   Welche Erkrankung, in welchem Jahr, bzw. seit wann:__________________________

3.10. **Unterleibserkrankungen, Erkrankungen der Geschlechtsorgane**  ja  nein

   Welche Erkrankung, in welchem Jahr, bzw. seit wann:__________________________

4. Haben Sie vor Ihrer Behandlung auf der Intensivstation **Sport getrieben**?
   ja  nein

   Wenn ja, welche Sportart?_________________________________________________

   Wie häufig?  einmal im Monat
   einmal in der Woche
   mehrmals in der Woche

**Vielen Dank!**
19.5 Abbreviations

ACTH  Adrenocorticotropic Hormone
ADR  Adverse Drug Reaction
AE  Adverse Event
AMG  German Drug Law
BfArM  Bundesinstitut für Arzneimittel und Medizinprodukte
CAP  Community acquired pneumonia
CI  Cardiac Index
COPD  Chronic Obstructive Pulmonary Disease
CRF  Case Report Form
CTCAE  Common Terminology Criteria for Adverse Events
CV  Curriculum Vitae
CVP  Central Venous Pressure
DAP  Diastolic Arterial Pressure
DMSB  Data Monitoring and Safety Board
EC  Ethics Committee
EGDT  Early Goal Directed Therapy
FFP  Fresh Frozen Plasma
GC  Glucocorticoids
GCP  Good Clinical Practice
GCS  Glasgow Coma Scale
GCP-V  GCP-Verordnung
GMP  Good Manufacturing Practice
HAP  Hospital acquired pneumonia
HIV  Humane Immunodeficiency Virus
HLA-DR  Human Leukocyte Antigen - DR
HR  Heart Rate
HrQoL  Health-related Quality of Life
ICH  International Conference on Harmonisation
ICU  Intensive Care Unit
IL  Interleukin
ISF  Investigator Site File
ITT  Intention-to-treat
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>KKSL</td>
<td>Koordinierungszentrum für Klinische Studien Leipzig</td>
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<tr>
<td>IdHC</td>
<td>Low dose hydrocortisone</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean Arterial Pressure</td>
</tr>
<tr>
<td>MRC</td>
<td>Medical Research Council</td>
</tr>
<tr>
<td>NO</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>PEEP</td>
<td>Positive Endexpiratory Pressure</td>
</tr>
<tr>
<td>PTSD</td>
<td>Post Traumatic Stress Syndrome</td>
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<tr>
<td>PP</td>
<td>Per-protocol</td>
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<tr>
<td>RBC</td>
<td>Red Blood Cell</td>
</tr>
<tr>
<td>RR</td>
<td>Riva Rochi</td>
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<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
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<tr>
<td>SAP</td>
<td>Systolic Arterial Pressure</td>
</tr>
<tr>
<td>ScvO₂</td>
<td>Central Venous Oxgen Saturation</td>
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<tr>
<td>SmPC</td>
<td>Summary of medicinal Product Characteristics</td>
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<tr>
<td>SOFA</td>
<td>Sepsis-related Organ Failure Assessment</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedures</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected Unexpected Serious Adverse Drug Reaction</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor Necrosis Factor</td>
</tr>
<tr>
<td>TMF</td>
<td>Trial Master File</td>
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</tbody>
</table>
19.6 Participating Sites

1. **Friedrich Schiller Universität**
   - Klinik für Anästhesie und Intensivtherapie
   - Erlanger Allee 101, 07747 Jena
   - Prof. Dr. Konrad Reinhart (Coordinating Investigator)

2. **Charité Universitätsmedizin Berlin**
   - Klinik für Anästhesiologie und operative Intensivmedizin
   - Campus Virchow-Klinikum und Campus Mitte
   - Augustenburger Platz 1, 13353 Berlin
   - PD Dr. Didier Keh (Scientific Coordinator)

3. **Universitätsklinikum Aachen**
   - Operative Intensivmedizin Erwachsene
   - Pauwelstr. 30, 52074 Aachen
   - PD Dr. Rolf Dembinski

4. **Charité Universitätsmedizin Berlin**
   - Med. Klinik mit Schwerpunkt Nephrologie und internistische Intensivmedizin
   - Campus Virchow-Klinikum
   - Augustenburger Platz 1, 13353 Berlin
   - Dr. Michael Oppert

5. **Charité Universitätsmedizin Berlin**
   - Med. Klinik mit Schwer. Infektiologie und Pneumologie
   - Campus Virchow-Klinikum und Campus Mitte
   - Charitéplatz 1, 10117 Berlin
   - Dr. Simone Rosseau

6. **Vivantes Humboldt-Klinikum**
   - Klinik für Innere Medizin - Kardiologie und konservative Intensivmedizin
   - Am Nordgraben 2, 13509 Berlin
   - Dr. Glenn Zachow
7. Vivantes Auguste-Viktoria-Klinikum  
Klinik für Anästhesiologie, Intensivmedizin und Schmerztherapie  
Rubensstr. 125, 12157 Berlin  
Prof. Dr. Peter Lehmkuhl

8. Vivantes Klinikum-Neukölln  
Klinik für Anästhesie, operative Intensivmedizin und Schmerztherapie  
Rudowerstr. 48, 12351 Berlin  
Prof. Dr. Herwig Gerlach

9. Vivantes Klinikum Neukölln  
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Rudowerstr. 48, 12351 Berlin  
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10. Vivantes Klinikum Hellersdorf  
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11. Vivantes Humboldt Klinikum  
Klinik für Anästhesie, operative Intensivmedizin und Schmerztherapie  
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12. Helios Klinikum Berlin Buch  
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13. St. Joseph Krankenhaus  
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Dr. Martin Schmutzler
14. Rheinische Friedrich-Wilhelms-Universität
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   Sigmund-Freud-Str. 25, 53105 Bonn
   Prof. Dr. Christian Putensen

15. KH Dresden-Friedrichstadt
   Klinik für Anästhesiologie und Intensivmedizin
   Friedrichstr. 41, 01067 Dresden
   Prof. Dr. Karl Friedrich Rothe

16. Universitätsklinik Carl Gustav Carus Dresden
   Klinik für Anästhesie und Intensivtherapie
   Fetscherstr. 74, 01307 Dresden
   Prof. Dr. Maximilian Ragaller

17. Helios Klinikum Erfurt
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   Prof. Dr. Andreas Meier-Hellmann

18. Universitätsklinikum Freiburg
   Anästhesiologische Universitätsklinik - Abteilung Anästhesiologie und Intensivtherapie
   Hugstetter Str. 55, 79106 Freiburg
   Prof. Dr. Karl-Heinz Kopp

19. Ernst Moritz Arndt Universität Greifswald
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20. KH Martha-Maria Halle-Döllau GmbH
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   Dr. Harald Fritz
21. Medizinische Fakultät der Martin-Luther-Universität Halle-Wittenberg -
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   Klinik für Anästhesiologie und operative Intensivmedizin
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   Prof. Dr. Joachim Radke

22. Universitätsklinikum Hamburg-Eppendorf
   Klinik für Intensivmedizin
   Martinstr. 52, 20246 Hamburg
   Dr. Axel Nierhaus

23. Universitätsklinikum Heidelberg
   Innere Medizin IV: Gastroenterologie, Infektionskrankheiten, Vergiftungen
   Im Neuenheimer Feld 410, 69120 Heidelberg
   Dr. Christoph Eisenbach

24. Klinik Heidenheim
   Klinik für Anästhesiologie und operative Intensivmedizin
   Schloßhaus Str. 100, 89522 Heidenheim
   Prof. Dr. Alexander Brinkmann

25. Klinik Henningsdorf der Oberhavel-Kliniken GmbH
   Abteilung für Anästhesie und Intensivmedizin
   Marwitzerstr. 91, 16716 Henningsdorf
   Dr. Andreas Lange

26. Klinikum Hildesheim GmbH
   Klinik für Kardiologie, Angiologie, Intensivmedizin (Medizinische Klinik I)
   Weinberg 1, 31134 Hildesheim
   Dr. Klaus-Friedrich Bodmann

27. Universitätsklinikum Schleswig-Holstein, Campus Kiel
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   Schwanenweg 21, 24105 Kiel
   Prof. Dr. Norbert Weiler
28. **Klinikum der Universität zu Köln**
   Medizinische Klinik I: Innere Medizin
   Kerpenerstr. 62, 50294 Köln
   Dr. Matthias Kochanek

29. **Kliniken der Stadt Köln - Krankenhaus Merheim**
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   Ostmerheimer Str. 200, 51058 Köln - Merheim
   Prof. Dr. Frank Wappler

30. **St. Elisabeth-Krankenhaus Köln-Hohenlind**
   Klinik für Anästhesiologie und operative Intensivmedizin
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31. **Universitätsklinikum Leipzig AöR**
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32. **Universitätsklinikum Mannheim**
   I. Medizinische Klinik: Kardiologie, Angiologie, Pneumologie
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33. **Universitätsklinikum Mannheim**
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34. **Universitätsklinikum Giessen und Marburg GmbH, Standort Marburg**
   Klinik für Innere Medizin, Schwerpunkt Pneumologie
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   PD Dr. Dr. Robert Bals
35. **Klinikum Nürnberg-Nord**  
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Prof.-Ernst-Nathan-Str. 1, 90419 Nürnberg  
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36. **Klinikum Ernst von Bergmann GmbH**  
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37. **Rostock Universitätsklinikum**  
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38. **Universitätsklinikum Ulm**  
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