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CADDIE2 - Evaluation of a clinical decision-support system for early detection of SIRS in pediatric intensive care: study protocol for a diagnostic study

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CADDIE2 - Evaluation of a clinical decision-support system for early detection of SIRS in pediatric intensive care: study protocol for a diagnostic study

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38 ABSTRACT

39 **Introduction:** Systemic inflammatory response syndrome (SIRS) is one of the most critical
40 indicators determining the clinical outcome of pediatric intensive care patients. Clinical
41 decision-support systems (CDSS) can be designed to support clinicians in detection and
42 treatment. However, the use of such systems is highly discussed as they are often associated
43 with accuracy problems and “alert fatigue”. We designed a CDSS for detection of pediatric
44 SIRS and hypothesize that a high diagnostic accuracy together with an adequate alerting will
45 accelerate the use. Our study will (1) determine the diagnostic accuracy of the CDSS
46 compared to “gold standard” decisions created by two, blinded experienced pediatricians, and
47 (2) compare the system’s diagnostic accuracy with that of routine clinical care decisions
48 compared to the same gold standard.

49 **Methods and analysis:** CADDIE2 is a single-arm, controlled, prospective diagnostic
50 accuracy study taking place at the Department of Pediatric Cardiology and Intensive Care
51 Medicine at the Hannover Medical School and represents the second step towards our vision
52 of cross-institutional and data-driven decision support for intensive care environments
53 (CADDIE). The study comprises (1) recruitment of up to 300 patients, (2) creation of “gold
54 standard” decisions, (3) routine SIRS assessments by physicians, (4) SIRS assessments by a
55 CDSS, and (5) statistical analysis with a modified approach for determining sensitivity and
56 specificity and comparing the accuracy results of the different diagnostic approaches.

57 **Ethics and dissemination:** Ethics approval was obtained at the study center. Results of the
58 main trial will be communicated via publication in a peer-reviewed journal.

59 **Discussion:** We present a study design for evaluating the diagnostic accuracy of a CDSS from
60 a routine clinical care perspective. CADDIE2 recruitment has been started successfully. In
61 case of positive study results, our evaluation will demonstrate the potentials of CDSS use and
62 foster the acceptance of such systems in routine decision-making.

63 **Trial registration:** ClinicalTrials.gov NCT03661450. Registered 07 September 2018.
64 Recruitment started August 1st, 2018, and it is expected to continue until February 2019.

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3 65 **Protocol version:** V1.0, 2018-Mar-06 Original
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6 66 **Keywords:** Clinical Decision Support Systems, Clinical Trial, Pediatric Intensive Care Units,
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8 67 Systemic Inflammatory Response Syndrome
9

10 68 **Abbreviations:** AMG, “Arzneimittelgesetz” (German), Medicinal Products Act; CADDIE,
11
12 69 Cross-institutional and Data-driven Decision Support for Intensive Care Environments;
13
14 70 CDSS, Clinical Decision-Support System; GCP, Good Clinical Practice; GMDS, German
15
16 71 Association for Medical Informatics, Biometry and Epidemiology; ICD, International
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18 72 Statistical Classification of Diseases and Related Health Problems; IPSCC, International
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20 73 Pediatric Sepsis Consensus Conference; PICU, Pediatric Intensive Care Unit; PDMS, Patient
21
22 74 Data Management System; RCT, Randomized Controlled Trials; SIRS, Systemic
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24 75 Inflammatory Response Syndrome; STARD, Standards for Reporting Diagnostic Accuracy
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26 76 Studies; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials.
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3 77 **ARTICLE SUMMARY**
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5 78 **Strengths and limitations of this study**
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8 80 • Related studies reached successful results in the context of decision-support for SIRS
9 81 detection, but due to the study design, the reported results often do not reflect the
10 82 usefulness of such systems in routine clinical care.
11
12 83 • We present an adjusted and novel approach for the course and the statistical analysis of
13 84 diagnostic studies from a more routine clinical care perspective, because our study
14 85 comprises
15
16 86 • (1) the validation of the clinical decision-support system in the comparison to the
17 87 assessment of two experienced clinicians by blinded chart review (“gold standard”) and
18
19 88 • (2) the comparison of the system’s diagnostic accuracy with the diagnostic accuracy of
20 89 assessments by clinicians working in routine clinical care and manually evaluating
21 90 patients.
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23 91 • Although our study does not comprise specific evaluations of CDSS user acceptance, it is
24 92 predestinated to present the potentials of CDSS use in routine clinical care and, thus, to
25 93 foster the willingness to trust the system in future.
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95 INTRODUCTION

96 The first definition of systemic inflammatory response syndrome (SIRS) and sepsis in adult
97 patients was made by the members of the “American College of Chest Physicians/Society of
98 Critical Care Medicine Consensus Conference Committee” in 1992. SIRS was described as a
99 “systemic inflammatory response to a variety of severe clinical insults”, sepsis on the other
100 hand was “the systemic response to infection” [1]. The criteria have been adapted to pediatric
101 patients by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005 [2].
102 According to this, SIRS was present if the patient presented two or more of the defined
103 criteria (at least an abnormal core temperature or leukocyte count are mandatory). The other
104 criteria include abnormal heart rate, respiratory rate and blood pressure. All these criteria are
105 specified depending on the age of the patient. According to the IPSCC, sepsis is defined as
106 SIRS in the presence of or as a result of suspected or proven infection. Although the definition
107 of SIRS is no longer taken into account in adult medicine, it is still relevant in pediatric
108 medicine. Pediatric patients with SIRS and sepsis are known to have a higher risk of
109 morbidity and mortality [3–6]. SIRS in pediatric patients also causes a significantly prolonged
110 stay in intensive care after cardiothoracic surgery [7] and entails an increased probability of
111 single and even multiple organ dysfunction [8].

112 Independent of the underlying disease and together with SIRS and sepsis, organ dysfunction
113 and failure represent the critical determinants of patient outcome in both adults and pediatric
114 intensive care medicine. Prevention and rapid effective treatment of multi organ dysfunction
115 and failure is crucial for survival. An optimization of the diagnostic and therapeutic workflow
116 is very likely to have an immense impact on clinical outcome of any critically ill patient. In
117 pediatric septic shock patients, every hour without appropriate treatment was associated with
118 an increased risk of death by 40% [9]. Conclusively, early recognition, evaluation and
119 treatment of pediatric SIRS and sepsis are vital for improved survival [10].

120 To assure that patients are treated with the best available approaches, evidence-based
121 medicine [11] in combination with personal expertise represent the current “gold standard” of
122 medical patient management. However, clinicians are often confronted with a stressful
123 environment, which fosters decision-making with a lower quality than aspired [12]. This is
124 particularly true for intensive care settings, in which clinicians are in need to make the
125 majority of their decisions under challenging conditions characterized by an high degree of
126 dynamics, uncertainty and risk, a need for immediate decisions and a vast amount of data.

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3 127 Altogether, these factors carry risk for medical errors and adverse effects on patient safety
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5 128 [13–15].

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7 129 To tackle these challenges, clinicians can be supported by clinical decision-support systems
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9 130 (CDSS) as these systems analyze, summarize and present crucial information. The growing
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11 131 digitalization of medical processes and patient care involves an immense amount of highly
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13 132 heterogeneous datasets carrying the potential to be valuable for other purposes than initially
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15 133 expected (*secondary use of data*): the design of systems that are able to efficiently reuse,
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17 134 analyze and present routine data, and thereby making data meaningful for clinical care, is
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19 135 fostered. CDSS are shining examples for systems processing clinical and non-clinical data and
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21 136 delivering an added value by detecting diseases, recommending therapies or uncovering yet
22
23 137 unknown disease patterns [16]. Particularly in sophisticated intensive care settings, the use of
24
25 138 highly developed automated patient data management systems (PDMS) allow the continuous
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27 139 recording of multiple clinical parameters and make high quality data available for the
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29 140 secondary use of data in CDSS.

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31 141 In our previous work, we designed a CDSS for the detection of SIRS in pediatric intensive
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33 142 care [17]. However, only when used in routine clinical care, the potential and benefits can be
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35 143 fully reached and translated into clinical care. Consequently, an extensive evaluation of the
36
37 144 system's diagnostic accuracy is needed to assure that users trust and use the system. This need
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39 145 is even aggravated in our context, because we strive for (1) using an automatic SIRS-labelling
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41 146 to train machine learning algorithms, and (2) reaching a self-learning system able to
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43 147 continuously process data and optimize the recommendations when used in routine care
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45 148 (*Learning Healthcare System*) [18]. In our previous work, we describe this approach for
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47 149 CDSS design, in which we denote the conduction of such a trial as **second** important step
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49 150 towards the vision of **cross-institutional and data-driven decision support for intensive care**
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51 151 **environments** (CADDIE, CADDIE2 for the presented trial) [18].

52
53 152 Related studies in the field of CDSS for SIRS and sepsis already reached satisfying results
54
55 153 [19–21]. However, due to the study designs, the reported results might not reflect the
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57 154 usefulness of the system in routine clinical care. Often, the coding of diagnoses as ICD
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59 155 (International Statistical Classification of Diseases and Related Health Problems) is used as
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156 “gold standard” against what the system's results are compared to. However, in ICD, episodes
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158 of SIRS and sepsis are not documented detailed enough, e.g. the time of occurrence as well as
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160 the clinical explanations are not described. Even though sometimes additional scores are used,
not all relevant episodes, which occurred during the intensive stay of a patient, can be

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3 160 reflected. Hence, systems evaluated with such an approach in fact have been successfully
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5 161 trained, but with respects to the ICD documentation and not routine decision-making.
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7 162 Additionally, in many studies, the study population is preselected and does only include
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9 163 patients who already have the diagnosis of sepsis on admission or provide a complete data set
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11 164 of all vital signs and documentations, which are required as input for the algorithm used. Such
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13 165 perfect data sets are often not available in routine clinical care settings.

14 166 The exploration of factors influencing a successful implementation of CDSS is an ubiquitous
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16 167 topic. In a recent literature review, Kilsdonk et al. [22] identified possible factors influencing
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18 168 an successful implementation of guideline-based CDSS. One of the aspects reported mostly,
19
20 169 deals with the *information quality of the system* and covers the relevance of data and messages
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22 170 delivered by the system [22]. This finding relates to a well-known and obviously still
23
24 171 unsolved issue called “alert fatigue” [23]. Other recent work published by Liberati et al. [24]
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26 172 describe the conduction of a qualitative study to identify different clusters of attitudes and
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28 173 barriers towards CDSS implementation. The authors describe that, together with a poor
29
30 174 integration in the clinical workflow, the “fear of experiencing excessive number of alerts”
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32 175 [24] is one of the factors hindering the willingness to trust systems and to believe in their
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34 176 unforeseen opportunities (*mutual adjustment*). This step is declared as one of the most
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36 177 challenging obstacles in CDSS adoption. It is suggested to integrate and evaluate the CDSS in
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38 178 routine clinical care and in cooperation with real users to overcome these limitations [24].

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40 179 Against the background of our CADDIE objectives and the reported findings on successful
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42 180 CDSS implementations, we conclude that there is a need for a CADDIE2 trial focusing on
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44 181 validating the CDSS for SIRS and sepsis detection in routine clinical care.

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183 **Study objectives and diagnostic approaches**

184 The **primary goal** of our study is the evaluation of the diagnostic accuracy of the CDSS for
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186 185 detecting SIRS in pediatric intensive care patients (*diagnostic approach 1*), in comparison to
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188 186 the assessments of two clinicians by blinded chart review. In case of disagreement, a third
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190 187 clinician will be consulted. The expert assessments will be treated as “gold standard” and
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192 188 comprise retrospective, extensive reviews and analyses of the patient’s data, state and
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194 189 documentations.

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196 190 The **secondary goal** of our study is to compare the diagnostic accuracy of the CDSS for
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198 191 detecting SIRS in pediatric intensive care patients evaluated against this gold standard, to the

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3 192 diagnostic accuracy of routine assessments of different clinicians working in routine clinical
4 193 care (*diagnostic approach II*) when compared to the same gold standard.

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8 9 195 **Trial design and study setting**

10 196 The CADDIE2 trial is designed as a single-arm, controlled, prospective diagnostic accuracy
11 197 study. Single study center is the Department of Pediatric Cardiology and Intensive Care
12 198 Medicine at the Hannover Medical School (monocentric). The estimated study duration is one
13 199 year. Our study does not contain comparisons between different patient populations (single-
14 200 arm) or interventions (no randomization). Each patient will be assessed by both diagnostic
15 201 approaches. Our study can be classified as a non-drug-study (according to the German
16 202 “Arzneimittelgesetz”, AMG; *Medicinal Products Act*) as it does not include interventions
17 203 with medicinal products.
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28 205 **METHODS AND ANALYSIS**

29 206 **Preceding studies**

30 207 For our study design, we can revert to a randomized controlled trial (RCT) with 807 pediatric
31 208 intensive care patients from the same ward as for the planned study. As a result of this RCT,
32 209 the expected SIRS prevalence on admission to PICU was reported as 5/100 and 20-10% of the
33 210 patients developed SIRS later on during their PICU stay [25]. Furthermore, we conducted a
34 211 proof-of-concept study focusing on the technical practicability [17]. The proof-of-concept
35 212 study yielded promising results for both the technical infrastructure and the accuracy of the
36 213 system (sensitivity of 1.00, specificity of 0.94) [17].
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46 215 **Recommendations and guidelines**

47 216 We reviewed ground work on study planning, national recommendations and templates of
48 217 ethics committees and associations, and followed the *Good Clinical Practice* (GCP) in non-
49 218 drug trials. We designed our study in accordance with the “Standards for Reporting
50 219 Diagnostic Accuracy Studies” (STARD) [26] and the “Standard Protocol Items:
51 220 Recommendations for Interventional Trials (SPIRIT) [27] guidelines (see Figure 1 in section
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56 221 *Timeline*, see additional file 1 for SPIRIT checklist).
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Patient population and eligibility criteria

All pediatric patients aged between 0 to 18 years admitted to the study center - independent of the gender, the underlying disease or the time of admission - will be asked for their consent to participate. Patients will be recruited continuously and included, if a positive consent is available, and their length of stay exceeds twelve hours.

The physicians who will evaluate the patients during routine care are mainly specialized pediatricians with experience in pediatric intensive care. There are always one more experienced physician (working in this PICU for over a year) and one less experienced physician (working in this PICU for less than a year) in charge. The reviewers who will perform the manual chart review for creating “gold standard” decisions are specialized pediatricians and very experienced in pediatric intensive care (working in this PICU for over three years).

235

Outcome measures

Sensitivity and specificity *on the level of patients* will be used as primary outcome measures. As second outcome measure, sensitivity and specificity also can be determined *on the level of intensive care days*.

240

Statistical analysis and Sample size calculation

For the primary outcome measure, sensitivity and specificity will be determined together with *Wald confidence intervals*. The comparison will be carried out by comparing the lower bound of the confidence interval with the null hypothesis. For the secondary outcome measure, sensitivity and specificity will be determined together with confidence intervals based on *general estimating equations*. Additionally, for the secondary goal of comparing the results to routine decisions, sensitivity and specificity will be compared by means of *McNemar tests* and confidence intervals constructed based on *general estimating equations*.

For analyzing the primary outcome measure, the assessment is carried out on the patient level.

This is the most conservative approach for estimating the diagnostic accuracy. The entire period of stay is considered and information are aggregated on the patient level. This leads to situations, which cannot be represented in only one cell of a contingency table. The classical four cases are amended by a new case, which occurs because the CDSS should not only

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2
3 254 correctly assess the occurrence of a SIRS event in general but with a correct timing (e.g. SIRS
4 255 event is identified within the correct shift). For example, this fifth case prevents that alert
5 256 firings on day 30 of the intensive care stay will be evaluated as *true positives* if the gold
6 257 standard reports a SIRS episode on day 2. Here, the CDSS did not identify the SIRS episode
7 258 within the correct shift. Thus, this case is used for the determination of both *false positives*
8 259 (day 30) and *false negatives* (day 2). Hence, the fifth case (false positive and false negative)
9 260 can be defined as follows: *the gold standard reports at least one SIRS episode, and the CDSS*
10 261 *detect SIRS episodes but (at least one) not within the same shift*. All other cases are defined as
11 262 usual (e.g. false positive: *the gold standard reports no SIRS episode but the CDSS detects one*
12 263 *or multiple SIRS episodes*).

13 264 Based on the different cases, the sensitivity and the specificity will be determined. For sample
14 265 size calculation, the results of the proof-of-concept study were used as a basis (sensitivity 1.00
15 266 and specificity 0.94, when calculating on the level of days). For this study with the modified
16 267 statistical analysis approach, a sensitivity of 90% (alternative hypothesis: 0.98, null
17 268 hypothesis: 0.90) and a specificity of 80% were expected (alternative hypothesis: 0.90, null
18 269 hypothesis: 0.80), with a given accuracy of estimate of 95% (type I error = 0.05) and a power
19 270 of 90% (chi square test). Consequently, 97 patients suffering from at least one SIRS episode
20 271 as well as 137 patients suffering from one or none SIRS episodes are required. Based on the
21 272 expected incidence and prevalence, at least 300 patients need to be considered.

22 273

23 274 **Timeline**

24 275 Before starting the study, the clinicians were introduced in the objectives and tasks. No
25 276 interventions, treatments or other care-related actions are prohibited during the trial and all
26 277 patients are treated with the standard procedures (including data collection and
27 278 measurements). Personal briefings on the new routine documentation were carried out during
28 279 this *pilot phase* (1 month). A designated assistant physician will present the study to the
29 280 patients, their parents or their legal guardians and ask for consent within the *recruiting phase*.
30 281 If no consent is available, the patient will not be recruited. Simultaneously, clinicians will
31 282 report their findings during their working shift per patient (routine assessments, *diagnostic*
32 283 *approach II*). The clinicians do not perform extensive analyses of documentations or reported
33 284 data (*assessment phase I*, with recruitment estimated as six months). It is documented whether
34 285 the patient suffered from SIRS, sepsis or organ dysfunction (via digital documentation form,
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3 286 see Figure 2). The first two weeks of this phase will be treated as test phase. If patients leave
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5 287 the ward after less than twelve hours, they will be excluded.

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7 288 Later on, two experienced clinicians will start with their weekly, extensive, blinded review
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9 289 and the definition of “gold standard” assessments per patient and per shift (*assessment phase*
10 290 *II*, at least three months). As soon as 97 patients suffering from one or more SIRS episodes as
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12 291 well as 137 patients suffering from one or none SIRS episodes have been identified, the
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14 292 recruitment will be terminated early on. Simultaneously, the data sets from all recruited
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16 293 patients will be integrated into a data repository to make them accessible for the CDSS. Then,
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18 294 the CDSS assessments per patients and per hour will start (*diagnostic approach I*). In the final
19 295 *analysis phase* (at least two months), the diagnostic accuracy of the CDSS will be evaluated
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21 296 by comparing the assessments to the “gold standard” decisions from the experts (primary goal
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23 297 of the study). Additionally, the diagnostic accuracy of the routine assessments will be
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25 298 determined by comparing them to the same “gold standard” decisions. Afterwards, the
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27 299 different accuracies can be compared (secondary goal of the study). Finally, the trial results
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29 300 will be communicated via publication in a peer-reviewed journal. Figure 1 visualizes the
30
31 301 different study episodes in a schematic diagram.

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33 **Figure 1:** Time schedule and study episodes for CADDIE2 trial

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36 305 **Recruitment and consent**

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38 306 Patients fulfilling the eligibility criteria, their parents or their legal guardians will receive
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40 307 information about the study during a personal discussion with a physician. Additionally, they
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42 308 will get an information letter together with the consent form (available in German, English,
43
44 309 Turkish and Arabic). Due to the pediatric specialty, we decided to create additional
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46 310 information sheets, one for children aged between 6 and 11, and one for children aged
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48 311 between 12 and 18. The families also will receive privacy statement forms (data protection,
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50 312 accessibility and confidentiality). An example consent form, including study information and
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52 313 privacy statements, can be found in additional file 2.

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315 **Patient involvement**

316 There were no funds or time allocated for patient and public involvement so we were unable
317 to involve patients. We intend to disseminate the results to the participants and will invite
318 patients to help us developing an appropriate method of dissemination.

319

320 **Data management and collection**

321 The CDSS is an application with interfaces to a data repository, which is based on an
322 semantic interoperability standard for clinical information representation (*openEHR* [28]). For
323 more information on data processing and managing, we refer to our previously published
324 paper [17]. For reasoning, the CDSS queries data from and stores results into the repository.
325 For the routine assessment (assessment phase I, diagnostic approach II), we created a
326 documentation form, which is based on the same interoperability standard and the same
327 interfaces to the data repository (see Figure 2). Thereby, all results (gold standard, diagnostic
328 approach I “CDSS”, diagnostic approach II “routine assessments”) will be available in the
329 same interoperable format. Patient data (identification, birthdate), intensive care parameters
330 (heart rate, respiratory rate, body temperature, leukocytes, neutrophils, mechanical ventilation,
331 cooling devices, pacemaker), alert parameters (SIRS, sepsis, organ dysfunction with duration,
332 beginning and end of the episode and shift), and general documentations of the patient
333 conditions, events or unintended effects will be documented and processed.

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339 **Figure 2:** Digital documentation form (based on openEHR data repository)

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343 **Data monitoring and auditing**

344 Accompanying quality assurance measures are continuously carried out to ensure high data
345 quality. Plausibility checks will be executed while integrating data into our repository (e.g.
346 simple counts can uncover whether data from the primary source systems is missing in the
347 data repository). Furthermore, the data set will be randomly reviewed by physicians to
guarantee the plausibility from a clinical perspective. By following the openEHR standard, we

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3 348 are able to automatically execute validation checks on specific parameters (e.g. definition of
4 349 ranges for specific values, or double data entries). Thereby, missing or wrong values will be
5 350 uncovered automatically when integrating the data sets or filling out the documentation form.
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7 351 The trial procedures will be monitored continuously by the authors as well as by designated
8
9 352 physicians and nurses. They will supervise the adherence to the study protocol, the procedures
10 353 for routine documentation and data integration, data quality and privacy.
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15 355 **Data protection: data access and confidentiality**

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17 356 We designed a data protection concept in cooperation with the local data security officer. The
18 357 concept defines pseudonymization and data access procedures, outlines the patient consent,
19 358 and explains technical security mechanisms. All data sets collected or created as part of this
20 359 trial are treated as strictly confidential. The data sets will be stored pseudonymized and in
21 360 secure conditions in the data repository located in the network of the Hannover Medical
22 361 School. To prevent unauthorized disclosure of patient information, it is only accessible for the
23 362 physicians and employees in charge for this study. Collected data from patients withdrawing
24 363 their consent (drop outs), will be completely deleted from the data repository. All study files,
25 364 the final trial data sets as well as the trial results will be archived for ten years in an approved
26 365 long-term repository and in accordance to the relevant legal and statutory requirements. The
27 366 patient will be informed about these procedures as well as their rights (including the
28 367 possibility to withdraw the consent and to obtain information about collected data sets at any
29 368 time), and will be asked to consent to these (see section Recruitment and consent).
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41 370 **Ethics and dissemination**

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44 371 All aspects are designed according to the General Data Protection Regulation from the
45 372 European Union (2016/679) and are accepted by the data security officer of the Hannover
46 373 Medical School. A positive vote of the ethics committee was given (No. 7804_BO_S_2018,
47 374 see Additional file 3). Further details on data protection aspects can be requested from the
48 375 authors. Results of the main trial will be communicated via publication in a peer-reviewed
49 376 journal. Furthermore, we intend to disseminate the results to the participants through an
50 377 appropriate method of dissemination to be defined.
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379 **DISCUSSION**

380 To be used in the long run, CDSS have to deliver relevant information in a timely manner and
381 at an adequate frequency. Current approaches for evaluating the usefulness of CDSS indeed
382 present positive results. However, due to a restricted study design, which is not designed
383 towards the specific conditions of daily work, evaluation results may not represent the
384 feasibility of the system in routine clinical care. Hence, with our work, we contribute a
385 modified study design for evaluating the diagnostic accuracy of a CDSS with a strong focus
386 on routine clinical care. We hypothesize that such an evaluation will demonstrate the
387 potentials of CDSS use in routine clinical care. In case of a positive study outcome, we will be
388 able to reason that our CDSS is not only feasible from a technical but also from a clinical
389 perspective as it supports clinicians in critical diagnostic decision-making. For evaluating the
390 diagnostic accuracy of a CDSS during a clinical trial, a so-called “gold standard” representing
391 the true state of the patient is required. However, in complex, knowledge-and experience-
392 based contexts as diagnostic decision-making, reproducible, objective and quantitative “gold
393 standards” are rare. In contrast to related trials, we use an excessive evaluation of the patient
394 by two experience clinicians as benchmark. To reduce possible biases, the clinicians are
395 blinded to each other as well as to the CDSS. In situations of disagreement, a third clinician
396 will be consulted, decisions will be revealed and a consensus decision will be reported. We
397 are aware that our approach is time-consuming requiring highly engaged clinicians. Because
398 of the stressful intensive care environment, assessments may be delayed, and thus, the
399 timeline of the study may not be adhered. For an early recognition of issues and study
400 monitoring at the ward, an assistant physician is in charge. Also the routine assessments of
401 clinicians have to be managed as they are at the same risk to be biased. Clinical
402 documentation might be handled more meticulous at the beginning and more careless in the
403 end of the study. With respect to the new documentation form, a positive feedback was given
404 within the test phase of the study. This might be due to the fact that clinicians were involved
405 in designing the form. Furthermore, the form was integrated in the PDMS used daily.
406 Together with the designated study monitor, this integration raised the satisfactory and the
407 utilization rate of the form as well as the adherence to the study protocol.

408 For sample size calculation, it might be possible that the incidence was overestimated, so that
409 in our settings more than 300 patients are needed to reach 97 patients suffering from at least
410 one SIRS episode. The recruitment will be continuously aligned towards the number of
411 recruited SIRS patients to be able to stop the recruitment as soon as the required number of

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3 412 SIRS patients has been reached. Our expected values for sensitivity and specificity are rather
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5 413 conservative because we decided to primarily use an equally conservative statistical analysis
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7 414 approach by calculating at the level of patients. However, the expected values are treated as
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9 415 acceptable in clinical routine as the diagnostic accuracy of the system will be over a critical
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11 416 minimum (and with respect to the aspired second goal of our study, even better than in
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13 417 clinical routine decision-making). At the same time, alert fatigue will be prevented because
14
15 418 specificity is equally high. Current CDSS often indeed present a higher sensitivity but a very
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17 419 low specificity. We are confident that our thoughts meet the need for an optimum balance
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19 420 between sensitivity and specificity, e.g. as reported by Coleman et al. [23]. Nevertheless, we
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21 421 will enhance our results with a more liberal analysis on the level of days.
22
23 422 Our study has been successfully started with recruitment according to this design and
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25 423 promises valuable results. When reaching a good diagnostic accuracy compared to the gold
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27 424 standard as well as advantages over the diagnostic accuracy of routine assessments, we are
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29 425 optimistic that our users are willing to trust and use the system in future.
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52 436 **STATEMENTS**

53 437 **Author Contributions**

54
55 438 AW was responsible for design and implementation of the presented clinical decision-support
56
57 439 system and the outline of the study protocol, and has drafted the manuscript. TJ provided
58
59
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3 440 clinical expertise for the use case and the design of the underlying knowledge model, leded
4 441 the proof-of-concept study and co-drafted the manuscript. AK was primarily responsible for
5 442 the design of the statistical analysis, the sample size calculation and the authoring of the
6 443 corresponding sections. BS and SM helped in the conception of the general study approach
7 444 but especially for definition of goals and outcome measures, timing and patient recruitment;
8 445 SM is responsible for patient recruitment and monitors the study at the ward. PB and MM
9 446 provided clinical expertise for study design, revised the manuscript critically, and gave
10 447 subject-specific advices as well as the final approval of the manuscript version to be
11 448 published. All authors read and approved the final manuscript.

449 **Competing interests**

450 The authors declare that they have no competing interests.

451 **Funding**

452 No funding to declare.

453 **Availability of data and material**

454 The datasets generated and/or analyzed during the current study are not publicly available due
455 to data privacy and security matters of patients but are available from the corresponding
456 author on reasonable request.

457 **Ethical approval and patient consent**

458 This diagnostic study received ethics approval from the Hannover Medical School Ethics
459 Committee (approval number 7804_BO_S_2018). The trial is registered with
460 ClinicalTrials.gov (NCT03661450).

461 Consent to participate will be given by the patients, by their parents or by their legal guardians
462 by signing a study consent form. All aspects are designed according to the General Data
463 Protection Regulation (EU) 2016/679 and are accepted by the data security officer of the
464 Hannover Medical School as well as by the Ethics Committee.

465 Protocol modifications will require a formal amendment to the protocol which will be
466 reported to the Hannover Medical School Ethics Committee for approval.

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2
3 467 **Acknowledgements**
4

5 468 We want to thank our colleagues from the ZIMt department for Educational and Scientific IT
6
7 469 Systems of the Hannover Medical School for supporting in matters of data access and
8
9 470 integration.
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For peer review only

471 **REFERENCES**

- 472 1 American College of Chest Physicians/Society of Critical Care Medicine Consensus
473 Conference: definitions for sepsis and organ failure and guidelines for the use of
474 innovative therapies in sepsis. *Critical care medicine* 1992;20(6):864–74. PubMed
475 PMID: 1597042.
- 476 2 Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference:
477 Definitions for sepsis and organ dysfunction in pediatrics*. *Pediatric Critical Care
478 Medicine* 2005;6(1):2–8. PubMed PMID: 15636651.
- 479 3 Wolfler A, Silvani P, Musicco M, et al. Incidence of and mortality due to sepsis, severe
480 sepsis and septic shock in Italian Pediatric Intensive Care Units: A prospective national
481 survey. *Intensive Care Med* 2008;34(9):1690–97. doi: 10.1007/s00134-008-1148-y.
- 482 4 Cvetkovic M, Lutman D, Ramnarayan P, et al. Timing of death in children referred for
483 intensive care with severe sepsis: Implications for interventional studies. *Pediatric
484 Critical Care Medicine* 2015;16(5):410–17. doi: 10.1097/PCC.0000000000000385.
- 485 5 Creedon JK, Vargas S, Asaro LA, et al. Timing of Antibiotic Administration in Pediatric
486 Sepsis. *Pediatr Emerg Care* 2018. doi: 10.1097/PEC.0000000000001663.
- 487 6 Kortz TB, Sawe HR, Murray B, et al. Clinical Presentation and Outcomes among
488 Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania. *Front Pediatr*
489 2017;5:278. doi: 10.3389/fped.2017.00278.
- 490 7 Boehne M, Sasse M, Karch A, et al. Systemic inflammatory response syndrome after
491 pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card
492 Surg* 2017;32(2):116–25. doi: 10.1111/jocs.12879.
- 493 8 Ganjoo S, Ahmad K, Qureshi UA, et al. Clinical Epidemiology of SIRS and Sepsis in
494 Newly Admitted Children. *Indian J Pediatr* 2015;82(8):698–702. doi: 10.1007/s12098-
495 014-1618-x.
- 496 9 Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic
497 shock by community physicians is associated with improved outcome. *Pediatrics*
498 2003;112(4):793–99. PubMed PMID: 14523168.
- 499 10 Paul R. Recognition, Diagnostics, and Management of Pediatric Severe Sepsis and
500 Septic Shock in the Emergency Department. *Pediatric Clinics of North America*
501 2018;65(6):1107–18. doi: 10.1016/j.pcl.2018.07.012.
- 502 11 Sackett DL. Evidence-based medicine. *Seminars in Perinatology* 1997;21(1):3–5.
503 PubMed PMID: 9190027.

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2
3 504 12 Zavala AM, Day GE, Plummer D, et al. Decision-making under pressure: Medical errors
4 in uncertain and dynamic environments. *Aust Health Rev* 2017. doi: 10.1071/AH16088.
5 505
6 506 13 Lighthall GK, Vazquez-Guillamet C. Understanding Decision Making in Critical Care.
7 *Clin Med Res* 2015;13(3-4):156–68. doi: 10.3121/cmr.2015.1289.
8 507
9 508 14 Castaneda C, Nalley K, Mannion C, et al. Clinical decision support systems for
10 improving diagnostic accuracy and achieving precision medicine. *J Clin Bioinforma*
11 509 2015;5:4. doi: 10.1186/s13336-015-0019-3.
12 510
13 511 15 Lincoln P, Manning M-J, Hamilton S, et al. A pediatric critical care practice group: use
14 of expertise and evidence-based practice in identifying and establishing "best" practice.
15 *Crit Care Nurse* 2013;33(2):85–87. doi: 10.4037/ccn2013740.
16 512
17 513 16 Shortliffe EH. Biomedical Informatics: Defining the Science and Its Role in Health
18 Professional Education. In: Hutchison D, Kanade T, Kittler J, et al., eds. Information
19 Quality in e-Health. Berlin, Heidelberg: Springer Berlin Heidelberg 2011:711–14.
20 514
21 515 17 Wulff A, Haarbrandt B, Tute E, et al. An interoperable clinical decision-support system
22 for early detection of SIRS in pediatric intensive care using openEHR. *Artif Intell Med*
23 516 2018;89:10–23. doi: 10.1016/j.artmed.2018.04.012.
24 517
25 518 18 Wulff A, Marschollek M. Learning Healthcare Systems in Pediatrics: Cross-Institutional
26 and Data-Driven Decision-Support for Intensive Care Environments (CADDIE). *Stud*
27 *Health Technol Inform* 2018;251:109–12. PubMed PMID: 29968614.
28 519
29 520 19 Faisal M, Scally A, Richardson D, et al. Development and External Validation of an
30 Automated Computer-Aided Risk Score for Predicting Sepsis in Emergency Medical
31 Admissions Using the Patient's First Electronically Recorded Vital Signs and Blood Test
32 Results. *Critical care medicine* 2018;46(4):612–18. doi:
33 521 10.1097/CCM.0000000000002967.
34 522
35 523 20 Austrian JS, Jamin CT, Doty GR, et al. Impact of an emergency department electronic
36 sepsis surveillance system on patient mortality and length of stay. *J Am Med Inform*
37 *Assoc* 2018;25(5):523–29. doi: 10.1093/jamia/ocx072.
38 524
39 525 21 Mao Q, Jay M, Hoffman JL, et al. Multicentre validation of a sepsis prediction algorithm
40 using only vital sign data in the emergency department, general ward and ICU. *BMJ*
41 *Open* 2018;8(1):e017833. doi: 10.1136/bmjopen-2017-017833.
42 526
43 527 22 Kilsdonk E, Peute LW, Jaspers MW. Factors influencing implementation success of
44 guideline-based clinical decision support systems: A systematic review and gaps
45 528
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3 536 analysis. *International Journal of Medical Informatics* 2017;98:56–64. doi:
4 10.1016/j.ijmedinf.2016.12.001.
5 537
6 538 23 Coleman JJ, van der Sijs H, Haefeli WE, et al. On the alert: Future priorities for alerts in
7 clinical decision support for computerized physician order entry identified from a
8 European workshop. *BMC Med Inform Decis Mak* 2013;13:111. doi: 10.1186/1472-
9 540 6947-13-111.
10 541
11 542 24 Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized
12 decision support systems in hospitals? A qualitative study and framework for
13 implementation. *Implement Sci* 2017;12(1):113. doi: 10.1186/s13012-017-0644-2.
14 543
15 544
16 545 25 Jack T, Boehne M, Brent BE, et al. In-line filtration reduces severe complications and
17 length of stay on pediatric intensive care unit: A prospective, randomized, controlled
18 trial. *Intensive Care Med* 2012;38(6):1008–16. doi: 10.1007/s00134-012-2539-7.
19 546
20 547
21 548 26 Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting
22 diagnostic accuracy studies: Explanation and elaboration. *BMJ Open*
23 2016;6(11):e012799. doi: 10.1136/bmjopen-2016-012799.
24 549
25 550
26 551 27 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration:
27 Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586.
28 552
29 553 28 Thomas Beale. Archetypes: Constraint-based Domain Models for Future-proof
30 Information Systems. In: Eleventh OOPSLA workshop on behavioral semantics: serving
31 the customer. Seattle, Washington, Boston: Northeastern University 2002:16–32.
32 554
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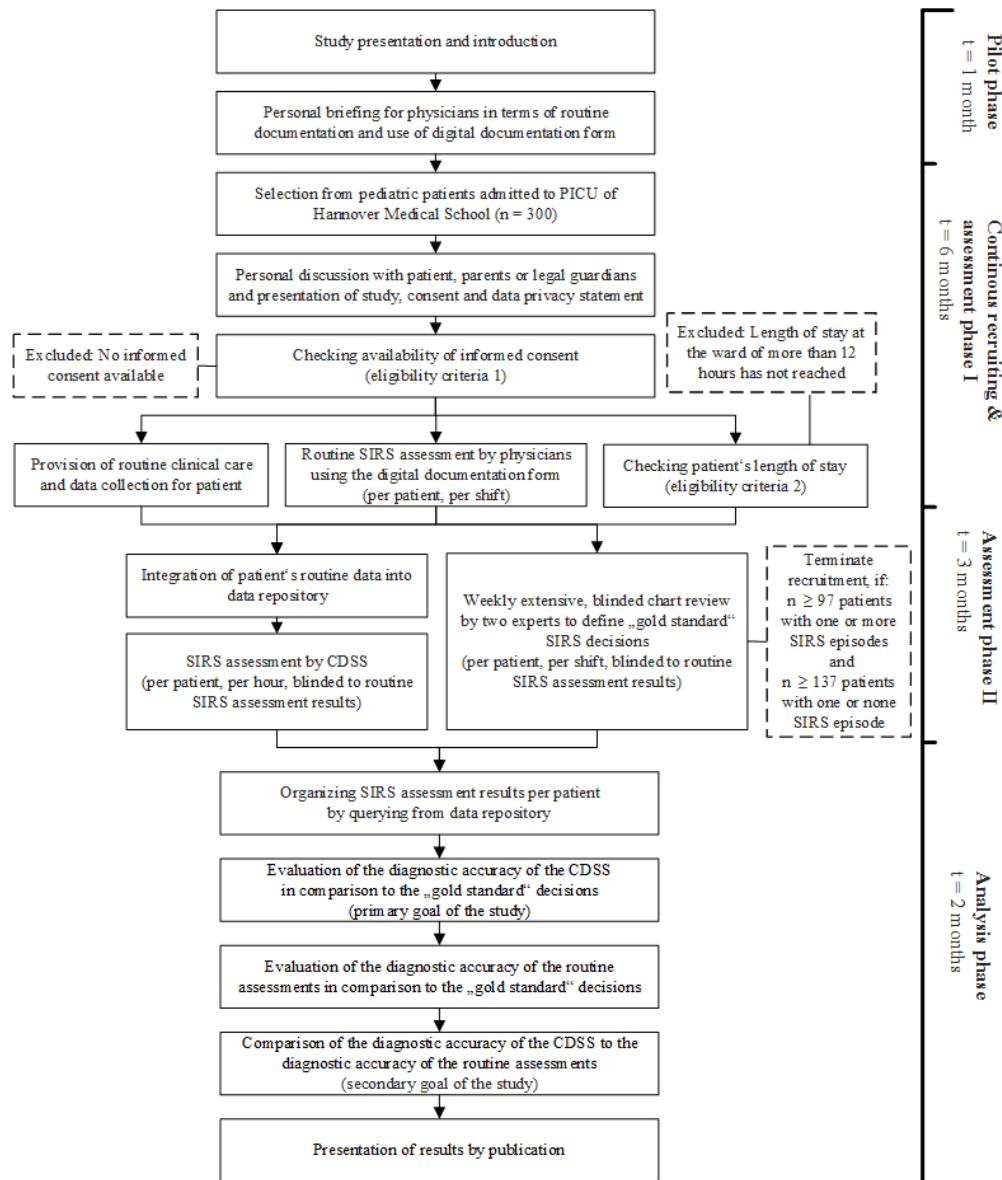


Figure 1: Time schedule and study episodes for CADDIE2 trial

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* Patient (Firstname Lastname):

* SIRS/No SIRS?: SIRS No SIRS

* Shift: Weekend day shift Weekend night shift Early shift
 Late shift Night shift

* on day:

Submit

* Patient (Firstname Lastname):

* SIRS/No SIRS?: SIRS No SIRS

* Shift: Weekend day shift Weekend night shift Early shift
 Late shift Night shift

* on day:

▼ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

* SIRS/Organdysfunction?: SIRS Organdysfunction

Origin: infectious noninfectious

Comment:

Submit

▼ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

* SIRS/Organdysfunction?: SIRS Organdysfunction

Type: respiratory cardiovascular renal hematologic
 hepatic

Comment:

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Figure 2: Digital documentation form (based on openEHR data repository)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___ 1 ___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___ 3 ___
	2b	All items from the World Health Organization Trial Registration Data Set	___ NA ___
Protocol version	3	Date and version identifier	___ 3 ___
Funding	4	Sources and types of financial, material, and other support	___ 18 ___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___ 1,18 ___
	5b	Name and contact information for the trial sponsor	___ NA ___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___ 18 ___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___ 9,15,16 ___

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____ 5,6,7__

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6 6b Explanation for choice of comparators _____ 5,6,7,8__

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8 Objectives 7 Specific objectives or hypotheses _____ 7,8__

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10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____ 8__

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____ 8__

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____ 9__

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered NA (no interventions, diagnostic study), alternative: _____ 8__

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29 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____ NA (each patient will be assessed by both diagnostic approaches), alternative: _____ 8__

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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____NA (no intervention, routine care), alternative: ____16____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____10____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	____9,10____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____10,11,12____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	____9,10____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____12,13____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	____NA____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	____NA____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____NA____

1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____7,11,16_
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4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____16_____
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8	Methods: Data collection, management, and analysis			
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10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13,14_
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA (no interventions)_
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18	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____13,14, 15_
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____9,10_
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26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
27				
28		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____NA_____
29				
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32	Methods: Monitoring			
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34	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
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40		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
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1	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____15_____
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4	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____15,16_____
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8	Ethics and dissemination			
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10	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____16, 18, 19, Additional file 3_____
11				
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14	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____19_____
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18	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____12,13_____
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22		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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25	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____13,15_____
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28	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18_____
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31	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____18_____
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34	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
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38	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____11,16_____
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1	31b	Authorship eligibility guidelines and any intended use of professional writers	_____18_____
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3	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
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5	Appendices		
6			
7	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
8			_____Additional
9			file 2_____
10	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable
11			_____NA_____
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13 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 14 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 15 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
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Patient Information (Parents)

Dear parents,

we would like to include your child in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

Your child was or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. Due to necessary monitoring and therapy we will gather laboratory results and vital signs continually.

During the clinical trial these laboratory and monitoring details will be analyzed with regard to a pronounced, generalized inflammatory reaction (Systemic inflammatory response syndrome (SIRS)) using the support of a computer-based system. The objective is to support the doctors in early recognition of SIRS.

The recognition of SIRS on a PICU is a complex task that is quite suitable for a Clinical Decision-Support System. SIRS is caused by different reasons, for example surgery, injuries or infection. It is a typical occurrence at PICU-patients and puts the patient under additional strain independent from the original reason for admittance. For diagnosing SIRS in paediatric patients correctly we have to find abnormalities in different vital signs and laboratory results which have age related reference values, making it an advanced task.

The development and clinical trial of a CDSS for SIRS in paediatric patients is the result of a cooperation between the Department of Paediatric Cardiology and Intensive Care Medicine of Medizinische Hochschule Hannover and the Peter L. Reichertz Institut für

1
2
3 Medizinische Informatik der Technischen Universität Braunschweig und der
4 Medizinischen Hochschule Hannover (PLRI).
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8 **Are there any risks by taking part in the clinical trial?**
9

10 The CDSS will only analyze data that is taken and saved during your child's admittance
11 on the PICU anyway. There won't be any additional blood tests, monitoring or
12 examinations. These standardized raised data will be saved in a pseudonymized way
13 that ensures the patient's privacy.
14
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17

18 **What happens if I don't agree to take part in the clinical trial?**
19

20 The whole team will respect your decision if you do not want your child to take part in
21 the clinical trial. This will not be evaluated or have any negative effect on your child's
22 treatment. You can also revoke your agreement anytime.
23
24
25
26

27 **Privacy Policy**
28

29 The data raised and saved for the trial are pseudonymized and it is impossible to
30 reconnect them to an individual. The data will be saved for 10 years and deleted
31 afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.
32
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36
37

38 I received the information and consent to the clinical trial mentioned above.
39

40 Yes

41 No
42
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46
47

48 _____
49 (Date and signature of the parent/legal guardian)
50
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56 _____
57 (Date and signature of the medical doctor)
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60

Patient Information (Patient)

Dear patient,

we would like to include you in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

You were or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. To treat you best we will monitor your vital signs as heartbeat, blood pressure and respiratory rate and take blood tests to monitor your white blood count and other inflammatory parameters. The results will be saved.

We know about the occurrence of extreme inflammatory reactions in paediatric patients. These can be caused by several reasons as surgery, injury or infection. We can measure these by changes in your vital signs, temperature or white blood count.

With a clinical trial something new is tested, for example some treatment. For this clinical trial your monitoring or vital sign data will be analyzed by a computer programme to support your doctors to detect changes that might be caused by an inflammatory reaction as soon as possible. The sooner we are aware we can adjust your treatment.

Are there any risks by taking part in the clinical trial?

The CDSS will only analyze data that is taken and saved during your admittance on the PICU anyway. There won't be any additional blood tests, monitoring or examinations. These standardized raised data will be saved in a pseudonymized way that ensures the patient's privacy.

What happens if I don't agree to take part in the clinical trial?

The whole team will respect your decision if you do not want to take part in the clinical trial. This will not be evaluated or have any negative effect on your treatment. You can also revoke your agreement anytime.

Privacy Policy

The data raised and saved for the trial are pseudonymized and it is impossible to reconnect them to an individual. The data will be saved for 10 years and deleted afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.

I received the information and consent to the clinical trial mentioned above.

Yes

No

(Date and signature of the patient)

(Date and signature of the medical doctor)



**Medizinische Hochschule
Hannover**

**Ethikkommission
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Prof. Dr. Stefan Engeli**

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20.06.2018/MLa

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Nr. 7804_BO_S_2018

Evaluation der diagnostischen Genauigkeit eines Clinical Decision-Support Systems (CDSS) zur Unterstützung der Erkennung von SIRS und Sepsis auf der pädiatrischen Intensivstation im Vergleich zu medizinischem Fachpersonal

Sehr geehrter Herr Kollege Jack,

die Mitglieder der Ethikkommission haben auf ihrer Sitzung am 21.03.2018 über o.g. Antrag beraten. Nach Eingang der gemäß unserem Schreiben vom 26.03.2018 überarbeiteten Unterlagen bestehen keine Bedenken gegenüber der Durchführung der Studie.

Die Ethikkommission weist darauf hin, dass die ärztliche und juristische Verantwortung bei den jeweiligen Prüfärzten verbleibt.

Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur cursorisch geprüft. Dieses Votum / diese Bewertung ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.

Mit besten Grüßen

Prof. Dr. Stefan Engeli
Vorsitzender der Ethikkommission

Folgende Mitglieder haben an der Beratung des o.g. Antrages mitgewirkt:

Prof. Dr. St. Engeli (Vorsitzender), Klinische Pharmakologie der MHH

PD Dr. U.-V. Albrecht, Stellv. Leiter des Peter L. Reichertz Institut für Medizinische Informatik

Prof. Dr. A. M. Das, Leiter der Pädiatrischen Stoffwechselmedizin, Klinik für Päd. Nieren-, Leber- und Stoffwechselerkrankungen, Zentrum Kinderheilkunde und Jugendmedizin der MHH

Dr. J. Graubner, Arzt für Allgemeinmedizin

Prof. Dr. Thomas Illig, Leiter Biobank (HUB)

Prof. Dr. A. Koch, Leiter der Abt. Biometrie der MHH

Frau Prof. Dr. B. Lohff, Em. Leiterin der Abt. Geschichte, Ethik und Philosophie der Medizin der MHH

Dr. Oliver Pramann, Fachanwalt für Medizinrecht

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Prof. Dr. Peter Vogt, Leiter der Klinik für Plastische und Wiederherstellungschirurgie, MHH

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CADDIE2 - Evaluation of a clinical decision-support system for early detection of systemic inflammatory response syndrome in pediatric intensive care: study protocol for a diagnostic study

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1 CADDIE2 - Evaluation of a clinical decision-support system for early 2 detection of systemic inflammatory response syndrome in pediatric 3 intensive care: study protocol for a diagnostic study

4
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38 ABSTRACT

39 **Introduction:** Systemic inflammatory response syndrome (SIRS) is one of the most critical
40 indicators determining the clinical outcome of pediatric intensive care patients. Clinical
41 decision-support systems (CDSS) can be designed to support clinicians in detection and
42 treatment. However, the use of such systems is highly discussed as they are often associated
43 with accuracy problems and “alert fatigue”. We designed a CDSS for detection of pediatric
44 SIRS and hypothesize that a high diagnostic accuracy together with an adequate alerting will
45 accelerate the use. Our study will (1) determine the diagnostic accuracy of the CDSS
46 compared to gold standard decisions created by two, blinded experienced pediatricians, and
47 (2) compare the system’s diagnostic accuracy with that of routine clinical care decisions
48 compared to the same gold standard.

49 **Methods and analysis:** CADDIE2 is a prospective diagnostic accuracy study taking place at
50 the Department of Pediatric Cardiology and Intensive Care Medicine at the Hannover Medical
51 School; it represents the second step towards our vision of cross-institutional and data-driven
52 decision support for intensive care environments (CADDIE). The study comprises (1)
53 recruitment of up to 300 patients (started *August 1, 2018*), (2) creation of gold standard
54 decisions (planned start date *February 1, 2019*), (3) routine SIRS assessments by physicians
55 (started with recruitment), (4) SIRS assessments by a CDSS (planned start date *February 1,*
56 *2019*), and (5) statistical analysis with a modified approach for determining sensitivity and
57 specificity and comparing the accuracy results of the different diagnostic approaches (planned
58 start date *May 1, 2019*).

59 **Ethics and dissemination:** Ethics approval was obtained at the study center (Ethics
60 Committee of the Hannover Medical School). Results of the main study will be
61 communicated via publication in a peer-reviewed journal.

62 **Trial registration:** ClinicalTrials.gov NCT03661450. Registered 07 September 2018.
63 Recruitment started August 1st, 2018, and it is expected to continue until February 2019.

64 **Protocol version:** V1.0, 2018-Mar-06 Original

65 **Keywords:** Clinical Decision Support Systems, Clinical Trial, Paediatric intensive & critical
66 care, Systemic Inflammatory Response Syndrome

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2
3 67 **Abbreviations:** CADDIE, Cross-institutional and Data-driven Decision Support for Intensive
4 Care Environments; CDSS, Clinical Decision-Support System; GCP, Good Clinical Practice;
5 68
6 69 GMDS, German Association for Medical Informatics, Biometry and Epidemiology; ICD,
7 International Statistical Classification of Diseases and Related Health Problems; IPSCC,
8 70 International Pediatric Sepsis Consensus Conference; PICU, Pediatric Intensive Care Unit;
9 71 PDMS, Patient Data Management System; RCT, Randomized Controlled Trials; SIRS,
10 72 Systemic Inflammatory Response Syndrome; STARD, Standards for Reporting Diagnostic
11 73 Accuracy Studies; SPIRIT, Standard Protocol Items: Recommendations for Interventional
12 74
13 75 Trials.
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76 **ARTICLE SUMMARY**

77 **Strengths and limitations of this study**

- 78
- 79 • Related studies reached successful results in the context of clinical decision-support
80 systems (CDSS) for SIRS detection, but due to the study design, the reported results often
81 do not reflect the usefulness of such systems in routine clinical care.
- 82 • We present an adjusted and novel approach for the design and the statistical analysis of
83 diagnostic studies for CDSSs from a more routine clinical care perspective, because our
84 study comprises
- 85 • (1) the validation of the clinical decision-support system in comparison to the assessment
86 of two experienced clinicians by blinded chart review (gold standard) and
- 87 • (2) the comparison of the system's diagnostic accuracy with the diagnostic accuracy of
88 real-time assessments by clinicians working in routine clinical care and manually
89 evaluating patients.
- 90 • Although our study does not comprise specific evaluations of CDSS user acceptance, it is
91 suited to present the potentials of CDSS use in routine clinical care and, thus, to foster the
92 willingness to trust the system in future.
- 93

94 INTRODUCTION

95 The first definition of systemic inflammatory response syndrome (SIRS) and sepsis was made
96 by the members of the “American College of Chest Physicians/Society of Critical Care
97 Medicine Consensus Conference Committee” in 1992. SIRS was described as a “systemic
98 inflammatory response to a variety of severe clinical insults”, sepsis on the other hand was
99 “the systemic response to infection” [1]. The criteria have been adapted to pediatric patients
100 by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005 [2]. According
101 to this, SIRS was present if the patient presented two or more of the defined age-dependent
102 criteria (at least an abnormal core temperature or leukocyte count). The other criteria include
103 abnormal heart rate and respiratory rate. According to the IPSCC, sepsis is defined as SIRS in
104 the presence of or as a result of suspected or proven infection. Although the definition of
105 SIRS is no longer taken into account for the sepsis diagnosis in adult medicine, it is still
106 relevant in pediatric medicine. Pediatric patients with SIRS and sepsis are known to have a
107 higher risk of morbidity and mortality [3-6]. SIRS in pediatric patients also causes a
108 significantly prolonged stay in intensive care after cardiothoracic surgery [7] and entails an
109 increased probability of organ dysfunctions [8].

110 Independent of the underlying disease and together with SIRS and sepsis, organ dysfunction
111 and failure represent the critical determinants of patient outcome in both adult and pediatric
112 medicine. Prevention and rapid effective treatment of multi-organ dysfunction and failure is
113 crucial for survival. An optimization of the diagnostic and therapeutic workflow is likely to
114 have an immense impact on clinical outcome of critically-ill patients. In pediatric septic shock
115 patients, every hour without appropriate treatment was associated with an increased chance of
116 death by 40% [9]. Conclusively, early recognition and treatment of pediatric SIRS and sepsis
117 are vital [10].

118 To assure that patients are treated with the best available approaches, evidence-based
119 medicine [11] together with personal expertise represent the current *gold standard* of medical
120 patient management. However, clinicians are often confronted with a stressful environment,
121 which fosters decision-making with a lower quality than aspired [12]. This is particularly true
122 for pediatric intensive care units (PICU), in which clinicians work under challenging
123 conditions characterized by a high degree of dynamics, uncertainty and risk, time pressure and
124 a vast amount of data. Altogether, these factors carry risk for medical errors and adverse
125 effects on patient safety [13-15].

1
2
3 126 To tackle these challenges, clinicians can be supported by clinical decision-support systems
4 (CDSS). The growing digitalization in medicine involves an immense amount of highly
5 127 (CDSS). The growing digitalization in medicine involves an immense amount of highly
6 heterogeneous datasets carrying the potential to be valuable for other purposes than initially
7 128 heterogeneous datasets carrying the potential to be valuable for other purposes than initially
8 expected (*secondary use of data*); the design of systems that are able to efficiently reuse and
9 129 expected (*secondary use of data*); the design of systems that are able to efficiently reuse and
10 assimilate routine data, and thereby making data meaningful for clinical care, is fostered.
11 130 assimilate routine data, and thereby making data meaningful for clinical care, is fostered.
12 CDSS are shining examples for systems processing clinical and non-clinical data and
13 131 CDSS are shining examples for systems processing clinical and non-clinical data and
14 delivering an added value by detecting diseases, recommending therapies or uncovering yet
15 132 delivering an added value by detecting diseases, recommending therapies or uncovering yet
16 unknown disease patterns [16]. Particularly in sophisticated intensive care settings, the use of
17 133 unknown disease patterns [16]. Particularly in sophisticated intensive care settings, the use of
18 highly developed patient data management systems (PDMS) allow the continuous recording
19 134 highly developed patient data management systems (PDMS) allow the continuous recording
20 of multiple clinical parameters and make high quality data available.
21 135 of multiple clinical parameters and make high quality data available.

22 136 In our previous work, we designed a rule-based and interoperable CDSS for the detection of
23 137 SIRS in pediatric intensive care[17]. The CDSS is able to retrieve and evaluate dynamic facts
24 138 as routinely and automatically measured parameters from the bedside monitors to detect SIRS
25 139 episodes. However, only when used in routine clinical care, the benefits can be translated into
26 140 clinical care. Consequently, an extensive evaluation of the system's diagnostic accuracy is
27 141 needed to assure that users will trust the system. This need is even aggravated in our context,
28 142 because we strive for (1) using an automatic SIRS-labelling to train machine learning
29 143 algorithms, and (2) reaching a self-learning system able to continuously process data and
30 144 optimize its algorithms when used in routine care (*Learning Healthcare System*) [18]. In our
31 145 previous work, we describe this approach for CDSS design, in which we denote the
32 146 conduction of such a study as **second** important step towards the vision of cross-institutional
33 147 **and data-driven decision support for intensive care environments (CADDIE2)** [18].

34 148 Related studies already reached satisfying results [19-21]. However, due to the study designs,
35 149 the reported results might not reflect the usefulness of the CDSS in routine clinical care.
36 150 Often, the coding of diagnoses as ICD (International Statistical Classification of Diseases and
37 151 Related Health Problems) is used as gold standard against which the system's results are
38 152 compared to. However, in ICD, episodes of SIRS and sepsis are not documented detailed
39 153 enough, e.g. the time of occurrence is not described. Even though sometimes additional scores
40 154 are used, not all relevant SIRS episodes can be reflected. Hence, systems evaluated with such
41 155 an approach in fact have been successfully trained, but with respects to the ICD
42 156 documentation and not routine decision-making. Additionally, the study population is often
43 157 very preselected and requires a complete data set of all parameters required as input for the
44 158 algorithm used. Such perfect data sets are often not available in clinical routine settings.

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3 159 The exploration of factors influencing a successful CDSS implementation is a ubiquitous
4
5 160 topic. In a recent literature review, Kilsdonk et al. [22] identified such factors for guideline-
6
7 161 based CDSS implementation. One of the aspects reported mostly deals with the *information*
8
9 162 *quality of the system* and covers the relevance of data and messages delivered by the system
10
11 163 [22]. This finding relates to a well-known and obviously still unsolved issue called “alert
12
13 164 fatigue” [23]. Other recent work published by Liberati et al. [24] describe the conduction of a
14
15 165 qualitative study to identify different clusters of attitudes and barriers towards CDSS
16
17 166 implementation. The authors describe that, together with a poor integration in the clinical
18
19 167 workflow, the “fear of experiencing excessive number of alerts” [24] is one of the factors
20
21 168 hindering the willingness to trust systems and to believe in their unforeseen opportunities
22
23 169 (*mutual adjustment*). This step is declared as one of the most challenging obstacles in CDSS
24
25 170 adoption. It is suggested to integrate and evaluate the CDSS in routine clinical care and with
26
27 171 real users to overcome these limitations [24].

28
29 172 Against the background of our CADDIE objectives and the findings on successful CDSS
30
31 173 implementations, we conclude that there is a need for a CADDIE2 trial focusing on validating
32
33 174 the CDSS for SIRS and sepsis detection in routine clinical care.

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35 175

36 176 **Study objectives and diagnostic approaches**

37 177 The **primary goal** is the evaluation of the diagnostic accuracy of the CDSS for detecting
38
39 178 SIRS in PICU patients (*diagnostic approach I*), in comparison to the assessments of two
40
41 179 clinicians by blinded chart review. In case of disagreement, a third clinician will be consulted.
42
43 180 The expert assessments will be treated as gold standard and contain retrospective, extensive
44
45 181 data analyses. These comprise evaluating all patients’ measurements, not restricted to the
46
47 182 SIRS parameters, including additional values for vital signs validated hourly by the attending
48
49 183 nurse.

50
51 184 The **secondary goal** is to compare the diagnostic accuracy of the CDSS for detecting SIRS in
52
53 185 PICU patients evaluated against this gold standard, to the diagnostic accuracy of routine
54
55 186 assessments of different clinicians working in routine clinical care (*diagnostic approach II*)
56
57 187 when compared to the same gold standard.

58
59 188
60

189 **Trial design and study setting**

190 The CADDIE2 study is designed as a single-arm, controlled, prospective diagnostic accuracy
191 study. Single study center is the Department of Pediatric Cardiology and Intensive Care
192 Medicine at the Hannover Medical School (monocentric). The estimated study duration is one
193 year. Our study does not contain comparisons between different patient populations (single-
194 arm) or interventions (no randomization). Each patient will be assessed by both diagnostic
195 approaches.

197 **METHODS AND ANALYSIS**

198 **Preceding studies**

199 We can take advantage of the results of a randomized controlled trial (RCT) with 807 PICU
200 patients from the same ward for the planned study. The expected SIRS prevalence on
201 admission to PICU was reported as 5/100; 20-10% of the patients developed SIRS later on
202 during their PICU stay [25]. Furthermore, we conducted a proof-of-concept study focusing on
203 the technical practicability of the CDSS, yielding at promising results for both the technical
204 infrastructure and the accuracy of the system (sensitivity of 1.00, specificity of 0.94) [17].

206 **Recommendations and guidelines**

207 We reviewed work on study planning, national recommendations and templates of ethics
208 committees and associations, and followed the Good Clinical Practice (GCP) in non-drug
209 trials. We designed our study in accordance with the “Standards for Reporting Diagnostic
210 Accuracy Studies” (STARD) [26] and the “Standard Protocol Items: Recommendations for
211 Interventional Trials (SPIRIT) [27] guidelines (see Figure 1, see additional file 1).

213 **Patient population and eligibility criteria**

214 All pediatric patients aged 0 to 18 years admitted to the study center - independent of the
215 gender, the underlying disease or the time of admission - will be asked for their consent to
216 participate. Patients will be recruited continuously and included, if a positive consent is
217 available; and their length of stay exceeds twelve hours because any patient developing SIRS
218 will not be discharged earlier.

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3 219 The physicians are specialized pediatricians with experience in pediatric intensive care. There
4
5 220 are always one experienced (working in this PICU for over a year) and one less experienced
6
7 221 physician (working in this PICU for less than a year) in charge. The reviewers who will
8
9 222 perform the manual chart review for creating gold standard decisions are specialized
10
11 223 pediatricians and very experienced (working in this PICU for over three years), able to
12
13 224 discriminate unsound and missing data.
14
15 225

16 226 **Outcome measures**

17 227 Sensitivity and specificity *on the level of patients* will be used as primary outcome measures.
18
19 228 As second outcome measure, sensitivity and specificity also can be determined *on the level of*
20
21 229 *intensive care days*.
22
23 230

25 231 **Statistical analysis and sample size calculation**

26 232 For the primary outcome measure, sensitivity and specificity will be determined together with
27
28 233 *Wald confidence intervals*. The comparison will be carried out by comparing the lower bound
29
30 234 of the confidence interval with the null hypothesis (which is, as described below in the sample
31
32 235 size calculation paragraph, a sensitivity of 0.90, and a specificity of 0.80). If the lower bound
33
34 236 of the 95% confidence intervals for sensitivity and specificity are both above the values of the
35
36 237 pre-defined null hypotheses, we will reject the null hypotheses. For the secondary outcome
37
38 238 measure, sensitivity and specificity will be determined together with confidence intervals
39
40 239 based on *general estimating equations*. Additionally, for the secondary goal of comparing the
41
42 240 diagnostic accuracy of the CDSS to the one of routine decisions (both when evaluated against
43
44 241 the gold standard), sensitivity and specificity values will be compared by means of *McNemar*
45
46 242 *tests* and confidence intervals constructed based on *general estimating equations*.

47 243 All analyses will be accompanied by secondary subgroup analyses, stratified e.g. by patients'
48
49 244 age, type of shift and clinical picture associated with SIRS detection (including SIRS, sepsis,
50
51 245 severe sepsis and septic shock). Factors that might modify the diagnostic accuracy of the
52
53 246 CDSS will thus be evaluated in an exploratory way, allowing a better understanding of
54
55 247 potential limitations of the system. SIRS prevalence and incidence will be monitored
56
57 248 throughout the pilot phase and the main phase of the study, and will be compared to pre-study
58
59 249 values in order to estimate the risk of a training effect on physicians' real-time diagnoses
60
250 caused by knowledge about the aims of this study.

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3 251 For analyzing the primary outcome measure, the assessment is carried out on the patient level.
4
5 252 This is challenging since the assessment is not cross-sectional (as e.g. if the unit of assessment
6
7 253 would be an hour respectively a shift) but needs to incorporate the complex longitudinal
8
9 254 course of potential assessments within one patient. It is, however, the clinically most
10
11 255 meaningful and the most conservative approach for estimating the diagnostic accuracy if
12
13 256 conducted correctly. In our case, the entire period of stay is considered and information are
14
15 257 aggregated on the patient level. Every person contributes (given that a correct diagnosis is
16
17 258 restricted to the period of an hour respectively a shift) parts of its period of stay to the
18
19 259 calculation of specificity independently of if the gold standard recorded a SIRS at some point
20
21 260 since everybody will have periods without SIRS diagnosis (which need to be classified as
22
23 261 well correctly by the CDSS). This leads to situations, which cannot be represented in only one
24
25 262 cell of a contingency table. The classical four cases are amended by a new case, which occurs
26
27 263 because the CDSS should assess the occurrence of a SIRS event with a correct timing (e.g.
28
29 264 SIRS event is identified within the correct hour respectively shift). For example, this fifth case
30
31 265 prevents that alert firings on day 30 of the intensive care stay will be evaluated as *true*
32
33 266 *positives* if the gold standard reports a SIRS episode on day 2. Here, the CDSS did not
34
35 267 identify the SIRS episode within the correct timing. Thus, this case is used for the
36
37 268 determination of both *false positives* (day 30, contributing to specificity) and *false negatives*
38
39 269 (day 2, contributing to sensitivity). Hence, the fifth case (false positive and false negative) can
40
41 270 be defined as follows: *the gold standard reports at least one SIRS episode, and the CDSS*
42
43 271 *detect SIRS episodes but (at least one) not within the same hour respectively shift.* All other
44
45 272 cases are defined as usual (e.g. false positive: *the gold standard reports no SIRS episode but*
46
47 273 *the CDSS detects one or multiple SIRS episodes).*

48
49 274 Based on the different cases, the sensitivity and the specificity will be determined
50
51 275 independently. For sample size calculation, the results of the proof-of-concept study were
52
53 276 used as a basis (sensitivity 1.00 and specificity 0.94, when calculating on the level of days).
54
55 277 For this study with the modified statistical analysis approach, a sensitivity of 90% (alternative
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57 278 hypothesis: 0.98, null hypothesis: 0.90) and a specificity of 80% (alternative hypothesis: 0.90,
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59 279 null hypothesis: 0.80) were chosen as a clinically relevant diagnostic accuracy, with a given
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280 accuracy of estimate of 95% (type I error = 0.05) and a power of 90% (chi square test).
281
282 Consequently, 97 patients suffering from at least one SIRS episode (for the estimation of
sensitivity) as well as 137 patients with or without SIRS episodes are required (for the

1
2
3 283 estimation of specificity). Based on the expected incidence and prevalence, at least 300
4 284 patients need to be considered.
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6
7 285

286 **Timeline**

287 Before study start, the clinicians were introduced in their tasks. No interventions, treatments
288 or other care-related actions are prohibited and patients are treated with standard procedures
289 (including data collection and measurements). Personal briefings on the routine
290 documentation were carried out during this *pilot phase* (July 1, 2018, estimated duration: 1
291 month, see Figure 1). A designated physician will present the study to the patients, their
292 parents or their legal guardians and ask for consent within the *recruiting phase* (August 1,
293 2018, estimated duration: 6 months). Simultaneously, clinicians will report their findings
294 during their working shift per patient (routine assessments, *diagnostic approach II*). The
295 clinicians do not perform extensive analyses of documentations or reported data (*assessment*
296 *phase I*, August 1, 2018, estimated duration: 6 months). In the routine assessments it is
297 documented whether the patient suffered from SIRS, sepsis or organ dysfunction (via digital
298 documentation form, see Figure 2). The first two weeks of this phase will be treated as test
299 phase.
300

301 Later on, two experienced clinicians will start with their weekly, extensive, blinded review
302 and the definition of gold standard assessments per patient and per hour (*assessment phase II*,
303 February 1, 2019, estimated duration: 3 months). As soon as 97 patients suffering from one or
304 more SIRS episodes as well as 137 patients with one or without SIRS episodes have been
305 identified, the recruitment will be terminated. Simultaneously, the data sets from all recruited
306 patients will be integrated into a data repository to make them accessible for the CDSS. The
307 CDSS assessments per patients and per hour will start (*diagnostic approach I*). In the final
308 *analysis phase* (May 1, 2019, estimated duration: 2 months), the diagnostic accuracy of the
309 CDSS will be evaluated by comparing the assessments to the gold standard decisions from the
310 experts (primary goal of the study). Additionally, the diagnostic accuracy of the routine
311 assessments will be determined by comparing them to the same gold standard decisions. The
312 different accuracies can be compared (secondary goal of the study). Finally, the study results
313 will be communicated via publication in a peer-reviewed journal.

313

314 **Recruitment and consent**

315 Eligible patients, their parents or their legal guardians will receive an information letter and a
316 consent form (available in German, English, Turkish and Arabic) during a personal discussion
317 with a physician. Additional information sheets for younger patients are available, one for
318 children aged six to eleven and one for children aged 12 to 18. The families will receive
319 privacy statement forms (data protection, accessibility and confidentiality; see additional file
320 2).

321

322 **Patient involvement**

323 There were no funds or time allocated for patient and public involvement so we were unable
324 to involve patients. We intend to disseminate the results to the participants and will invite
325 patients to help us developing an appropriate method of dissemination.

326

327 **Data management and collection**

328 The CDSS is an application with interfaces to a data repository, which is based on an
329 semantic interoperability standard for clinical information representation (*openEHR* [28]). For
330 more information, we refer to [17]. For the routine assessment (assessment phase I, diagnostic
331 approach II), we created a documentation form, which is based on the same interoperability
332 standard and the same interfaces to the data repository (see Figure 2). Thereby, all results
333 (gold standard, diagnostic approach I “CDSS”, diagnostic approach II “routine assessments”)
334 will be available in the same format. Patient data (identification, birthdate), intensive care
335 parameters (heart rate, respiratory rate, body temperature, leukocytes, neutrophils, mechanical
336 ventilation, cooling devices, pacemaker), alert parameters (SIRS, sepsis, organ dysfunction
337 with duration, beginning and end of the episode and shift), and general documentations of the
338 patient conditions, events or unintended effects will be documented and processed.

339

340

341 **Data monitoring and auditing**

342 Quality assurance measures are continuously carried out. Plausibility checks will be executed
343 while integrating data into our repository (e.g. simple counts to can uncover whether data
344 from the primary source is missing in the repository). Furthermore, the data set will be
345 reviewed by physicians with respect to randomly selected observations to guarantee the

1
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3 346 plausibility from a clinical perspective. By following the openEHR standard, we are able to
4
5 347 automatically execute validation checks to uncover missing or wrong values when integrating
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7 348 the data sets or filling out the documentation form (e.g. definition of ranges for specific
8
9 349 values, or double data entries). The study procedures will be monitored by the authors as well
10
11 350 as by designated physicians and nurses. They will supervise the adherence to the study
12
13 351 protocol, the procedures for routine documentation and data integration, data quality and
14
15 352 privacy.

15 353

17 354 **Data protection: data access and confidentiality**

19 355 We designed a data protection concept in cooperation with the local data security officer. The
20
21 356 concept defines pseudonymization and data access procedures, outlines the patient consent,
22
23 357 and explains technical security mechanisms. All data sets collected or created as part of this
24
25 358 study are treated as strictly confidential. The data sets will be stored pseudonymized and in
26
27 359 secure conditions in the data repository located in the network of the Hannover Medical
28
29 360 School. To prevent unauthorized disclosure of patient information, it is only accessible for the
30
31 361 physicians and employees in charge of this study. Collected data from patients withdrawing
32
33 362 their consent (drop outs), will be completely deleted from the data repository. All study files,
34
35 363 the final study data sets as well as the study results will be archived for ten years in an
36
37 364 approved long-term repository and in accordance to the relevant legal and statutory
38
39 365 requirements. The patient will be informed about these procedures as well as their rights
40
41 366 (including the possibility to withdraw the consent and to obtain information about collected
42
43 367 data sets at any time), and will be asked to consent to these.

42 368

44 369 **Ethics and dissemination**

46 370 All aspects are designed according to the General Data Protection Regulation from the
47
48 371 European Union (2016/679) and are accepted by the data security officer of the Hannover
49
50 372 Medical School. A positive vote of the ethics committee was given (No. 7804_BO_S_2018,
51
52 373 see additional file 3). Further details on data protection aspects can be requested from the
53
54 374 authors. Results of the main study will be communicated via publication in a peer-reviewed
55
56 375 journal. We intend to disseminate the results to the participants through an appropriate
57
58 376 method of dissemination to be defined.

58 377

DISCUSSION

To be used in the long run, CDSSs have to deliver relevant information in a timely manner and at an adequate frequency. Current approaches for evaluating the usefulness of CDSS indeed present positive results. However, due to a restricted study design not designed towards daily work conditions, results may not represent the system feasibility in routine clinical care. With our work, we contribute a modified study design for evaluating the diagnostic accuracy of a CDSS with a strong focus on routine clinical care. We hypothesize that such an evaluation will demonstrate the potentials of CDSS use in routine clinical care. In case of a positive study outcome, we will be able to reason that our CDSS is not only feasible from a technical but also from a clinical perspective as it supports clinicians in critical diagnostic decision-making. For evaluation, a so-called gold standard representing the true state of the patient is required. However, in complex, knowledge-and experience-based contexts as diagnostic decision-making, reproducible, objective and quantitative “gold standards” are rare. We use an excessive evaluation of the patient data by two experience clinicians as benchmark. To reduce possible biases, the clinicians are blinded to each other and to the CDSS. In situations of disagreement, a third clinician will be consulted, decisions will be revealed and a consensus decision will be reported. We are aware that our approach is time-consuming requiring highly engaged clinicians. Because of the stressful PICU environment, assessments may be delayed, and thus, the study timeline may not be adhered. For an early recognition of issues and study monitoring at the ward, an assistant physician is in charge. Also the routine assessments of clinicians have to be managed as they are at the same risk to be biased. Clinical documentation might be handled more meticulous at the beginning and more careless in the end of the study. To prevent the latter, the new documentation form was designed in cooperation with the users and integrated in the PDMS used daily. Together with the designated study monitor, this integration raised the satisfactory and the utilization rate of the form as well as the adherence to the study protocol.

For sample size calculation, it might be possible that the incidence was overestimated, so that in our settings more than 300 patients are needed to reach 97 patients suffering from at least one SIRS episode. The recruitment will be continuously aligned towards the number of recruited SIRS patients to be able to stop the recruitment as soon as the required number has been reached. Our expected values for sensitivity and specificity are rather conservative because we decided to primarily use an equally conservative statistical analysis approach. However, the expected values are treated as acceptable in clinical routine as the diagnostic

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3 411 accuracy of the system will be over a critical minimum (and with respect to the aspired
4 412 second goal of our study, even better than in clinical routine decision-making). At the same
5 413 time, alert fatigue will be prevented because specificity is equally high. We are confident that
6 414 our thoughts meet the need for an optimum balance between sensitivity and specificity, e.g. as
7 415 reported by Coleman et al. [23]. Nevertheless, we will enhance our results with a more liberal
8 416 analysis on the level of days.

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13 417 Our study has been successfully started with recruitment according to this design and
14 418 promises valuable results. When reaching a good diagnostic accuracy compared to the gold
15 419 standard as well as advantages over the diagnostic accuracy of routine assessments, we are
16 420 optimistic that our users are willing to trust and use the system in future. Moreover, this will
17 421 allow the conduction of future studies as for example the evaluation of patient outcomes, user
18 422 acceptability, or real-time performance of the system.

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33 434 **STATEMENTS**

34 435 **Author Contributions**

35 436 AW was responsible for design and implementation of the presented clinical decision-support
36 437 system and the outline of the study protocol, and has drafted the manuscript. TJ provided
37 438 clinical expertise for the use case and the design of the underlying knowledge model, leaded
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3 439 the proof-of-concept study and co-drafted the manuscript. AK was primarily responsible for
4
5 440 the design of the statistical analysis, the sample size calculation and the authoring of the
6
7 441 corresponding sections. BS and SM helped in the conception of the general study approach
8
9 442 but especially for definition of goals and outcome measures, timing and patient recruitment;
10
11 443 SM is responsible for patient recruitment and monitors the study at the ward. PB and MM
12
13 444 provided clinical expertise for study design, revised the manuscript critically, and gave
14
15 445 subject-specific advices as well as the final approval of the manuscript version to be
16
17 446 published. All authors read and approved the final manuscript.

18 447 **Competing interests**

19
20 448 The authors declare that they have no competing interests.

21 22 449 **Funding**

23
24 450 No funding to declare.

25 26 451 **Availability of data and material**

27
28 452 The datasets generated and/or analyzed during the current study are not publicly available due
29
30 453 to data privacy and security matters of patients but are available from the corresponding
31
32 454 author on reasonable request.

33 34 455 **Ethical approval and patient consent**

35
36 456 This diagnostic study received ethics approval from the Hannover Medical School Ethics
37
38 457 Committee (approval number 7804_BO_S_2018). The trial is registered with
39
40 458 ClinicalTrials.gov (NCT03661450).

41
42 459 Consent to participate will be given by the patients, by their parents or by their legal guardians
43
44 460 by signing a study consent form. All aspects are designed according to the General Data
45
46 461 Protection Regulation (EU) 2016/679 and are accepted by the data security officer of the
47
48 462 Hannover Medical School as well as by the Ethics Committee.

49
50 463 Protocol modifications will require a formal amendment to the protocol which will be
51
52 464 reported to the Hannover Medical School Ethics Committee for approval.

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2
3 465 **Acknowledgements**
4

5 466 We want to thank our colleagues from the ZIMt department for Educational and Scientific IT
6
7 467 Systems of the Hannover Medical School for supporting in matters of data access and
8
9 468 integration.
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For peer review only

469 **REFERENCES**

- 470 1 American College of Chest Physicians/Society of Critical Care Medicine Consensus
471 Conference: definitions for sepsis and organ failure and guidelines for the use of
472 innovative therapies in sepsis. *Crit Care Med* 1992;20(6):864–74. PubMed PMID:
473 1597042.
- 474 2 Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference:
475 Definitions for sepsis and organ dysfunction in pediatrics*. *Pediatr Crit Care Med*
476 2005;6(1):2–8. doi: 10.1097/01.PCC.0000149131.72248.E6.
- 477 3 Wolfler A, Silvani P, Musicco M, et al. Incidence of and mortality due to sepsis, severe
478 sepsis and septic shock in Italian Pediatric Intensive Care Units: A prospective national
479 survey. *Intensive Care Med* 2008;34(9):1690–97. doi: 10.1007/s00134-008-1148-y.
- 480 4 Cvetkovic M, Lutman D, Ramnarayan P, et al. Timing of death in children referred for
481 intensive care with severe sepsis: Implications for interventional studies. *Pediatric
482 Critical Care Medicine* 2015;16(5):410–17. doi: 10.1097/PCC.0000000000000385.
- 483 5 Creedon JK, Vargas S, Asaro LA, et al. Timing of Antibiotic Administration in Pediatric
484 Sepsis. *Pediatr Emerg Care* 2018. doi: 10.1097/PEC.0000000000001663.
- 485 6 Kortz TB, Sawe HR, Murray B, et al. Clinical Presentation and Outcomes among
486 Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania. *Front Pediatr*
487 2017;5:278. doi: 10.3389/fped.2017.00278.
- 488 7 Boehne M, Sasse M, Karch A, et al. Systemic inflammatory response syndrome after
489 pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card
490 Surg* 2017;32(2):116–25. doi: 10.1111/jocs.12879.
- 491 8 Ganjoo S, Ahmad K, Qureshi UA, et al. Clinical Epidemiology of SIRS and Sepsis in
492 Newly Admitted Children. *Indian J Pediatr* 2015;82(8):698–702. doi: 10.1007/s12098-
493 014-1618-x.
- 494 9 Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic
495 shock by community physicians is associated with improved outcome. *Pediatrics*
496 2003;112(4):793–99. doi: 10.1542/peds.112.4.793.
- 497 10 Paul R. Recognition, Diagnostics, and Management of Pediatric Severe Sepsis and
498 Septic Shock in the Emergency Department. *Pediatr Clin North Am* 2018;65(6):1107–
499 18. doi: 10.1016/j.pcl.2018.07.012.
- 500 11 Sackett DL. Evidence-based medicine. *Semin Perinatol* 1997;21(1):3–5. doi: 10.1016/
501 S0146-0005(97)80013-4.

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2
3 502 12 Zavala AM, Day GE, Plummer D, et al. Decision-making under pressure: Medical errors
4 in uncertain and dynamic environments. *Aust Health Rev* 2017. doi: 10.1071/AH16088.
5 503
6 504 13 Lighthall GK, Vazquez-Guillamet C. Understanding Decision Making in Critical Care.
7 *Clin Med Res* 2015;13(3-4):156–68. doi: 10.3121/cm.2015.1289.
8 505
9 506 14 Castaneda C, Nalley K, Mannion C, et al. Clinical decision support systems for
10 improving diagnostic accuracy and achieving precision medicine. *J Clin Bioinforma*
11 507
12 508 2015;5:4. doi: 10.1186/s13336-015-0019-3.
13
14 509 15 Lincoln P, Manning M-J, Hamilton S, et al. A pediatric critical care practice group: use
15 of expertise and evidence-based practice in identifying and establishing "best" practice.
16 510
17 511 *Crit Care Nurse* 2013;33(2):85–87. doi: 10.4037/ccn2013740.
18
19 512 16 Shortliffe EH. Biomedical Informatics: Defining the Science and Its Role in Health
20 Professional Education. In: Hutchison D, Kanade T, Kittler J, et al., eds. Information
21 513
22 514 Quality in e-Health. Berlin, Heidelberg: Springer Berlin Heidelberg 2011:711–14.
23
24 515 17 Wulff A, Haarbrandt B, Tute E, et al. An interoperable clinical decision-support system
25 for early detection of SIRS in pediatric intensive care using openEHR. *Artif Intell Med*
26 516
27 517 2018;89:10–23. doi: 10.1016/j.artmed.2018.04.012.
28
29 518 18 Wulff A, Marschollek M. Learning Healthcare Systems in Pediatrics: Cross-Institutional
30 and Data-Driven Decision-Support for Intensive Care Environments (CADDIE). *Stud*
31 519
32 520 *Health Technol Inform* 2018;251:109–12. doi:10.3233/978-1-61499-880-8-109
33
34 521 19 Faisal M, Scally A, Richardson D, et al. Development and External Validation of an
35 Automated Computer-Aided Risk Score for Predicting Sepsis in Emergency Medical
36 522
37 523 Admissions Using the Patient's First Electronically Recorded Vital Signs and Blood Test
38 Results. *Crit Care Med* 2018;46(4):612–18. doi: 10.1097/CCM.0000000000002967.
39 524
40 525 20 Austrian JS, Jamin CT, Doty GR, et al. Impact of an emergency department electronic
41 sepsis surveillance system on patient mortality and length of stay. *J Am Med Inform*
42 526
43 527 *Assoc* 2018;25(5):523–29. doi: 10.1093/jamia/ocx072.
44
45 528 21 Mao Q, Jay M, Hoffman JL, et al. Multicentre validation of a sepsis prediction algorithm
46 using only vital sign data in the emergency department, general ward and ICU. *BMJ*
47 529
48 530 *Open* 2018;8(1):e017833. doi: 10.1136/bmjopen-2017-017833.
49
50 531 22 Kilsdonk E, Peute LW, Jaspers MW. Factors influencing implementation success of
51 guideline-based clinical decision support systems: A systematic review and gaps
52 532
53 533 analysis. *Int J Med Inform* 2017;98:56–64. doi: 10.1016/j.ijmedinf.2016.12.001.
54
55
56
57
58
59
60

- 1
2
3 534 23 Coleman JJ, van der Sijs H, Haefeli WE, et al. On the alert: Future priorities for alerts in
4
5 535 clinical decision support for computerized physician order entry identified from a
6
7 536 European workshop. *BMC Med Inform Decis Mak* 2013;13:111. doi: 10.1186/1472-
8
9 537 6947-13-111.
- 10 538 24 Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized
11
12 539 decision support systems in hospitals? A qualitative study and framework for
13
14 540 implementation. *Implement Sci* 2017;12(1):113. doi: 10.1186/s13012-017-0644-2.
- 15 541 25 Jack T, Boehne M, Brent BE, et al. In-line filtration reduces severe complications and
16
17 542 length of stay on pediatric intensive care unit: A prospective, randomized, controlled
18
19 543 trial. *Intensive Care Med* 2012;38(6):1008–16. doi: 10.1007/s00134-012-2539-7.
- 20 544 26 Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting
21
22 545 diagnostic accuracy studies: Explanation and elaboration. *BMJ Open*
23
24 546 2016;6(11):e012799. doi: 10.1136/bmjopen-2016-012799.
- 25 547 27 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration:
26
27 548 Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586.
- 28
29 549 28 Thomas Beale. Archetypes: Constraint-based Domain Models for Future-proof
30
31 550 Information Systems. In: Eleventh OOPSLA workshop on behavioral semantics: serving
32
33 551 the customer. Seattle, Washington, Boston: Northeastern University 2002:16–32.
34
35 552
36 553
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41
42 557
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569 **Figure 1:** Time schedule and study episodes for CADDIE2 trial

570 **Figure 2:** Digital documentation form (based on openEHR data repository)

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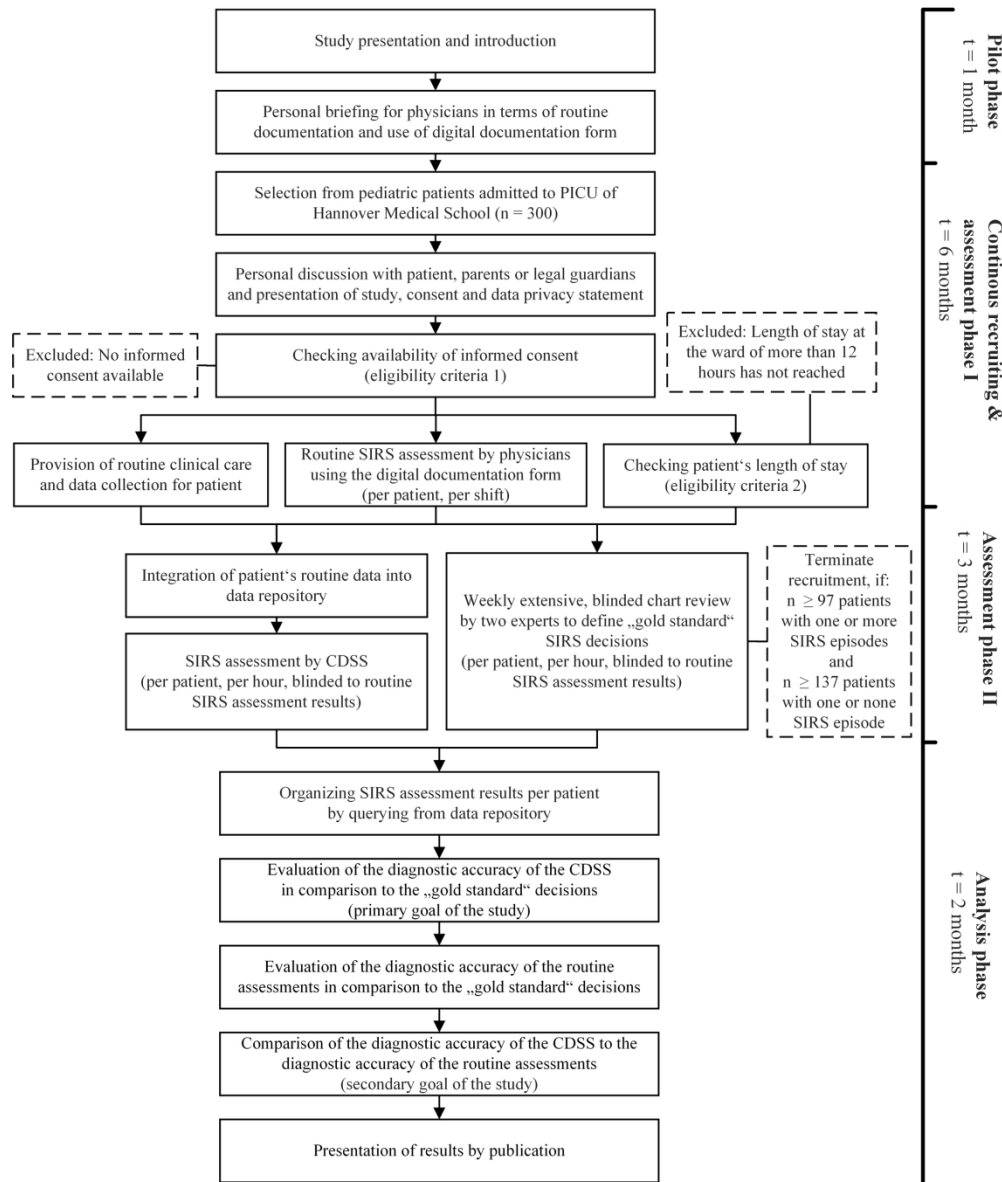


Figure 1: Time schedule and study episodes for CADDIE2 trial

208x245mm (300 x 300 DPI)

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7 * Patient (Firstname Lastname):

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9 * SIRS/No SIRS?: SIRS No SIRS

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11 * Shift: Weekend day shift Weekend night shift Early shift
12 Late shift Night shift

13

14 * on day:

15

16

17 * Patient (Firstname Lastname):

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19 * SIRS/No SIRS?: SIRS No SIRS

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21 * Shift: Weekend day shift Weekend night shift Early shift
22 Late shift Night shift

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24 * on day:

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26 ∨ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

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28 * SIRS/Organdysfunction?: SIRS Organdysfunction

29

30 Origin: infectious noninfectious

31

32 Comment:

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34 ∨ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

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36 * SIRS/Organdysfunction?: SIRS Organdysfunction

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38 Type: respiratory cardiovascular renal hematologic
39 hepatic

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41 Comment:

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Figure 2: Digital documentation form (based on openEHR data repository)

90x109mm (300 x 300 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3___
	2b	All items from the World Health Organization Trial Registration Data Set	___NA___
Protocol version	3	Date and version identifier	___3___
Funding	4	Sources and types of financial, material, and other support	___18___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1,18___
	5b	Name and contact information for the trial sponsor	___NA___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___18___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___9,15,16_

1 **Introduction**

2

3 Background and 6a Description of research question and justification for undertaking the trial, including summary of relevant _____5,6,7__

4 rationale studies (published and unpublished) examining benefits and harms for each intervention

5

6 6b Explanation for choice of comparators _____5,6,7,8__

7

8 Objectives 7 Specific objectives or hypotheses _____7,8_____

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group),

11 allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____8_____

12

13

14 **Methods: Participants, interventions, and outcomes**

15

16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will _____8_____

17 be collected. Reference to where list of study sites can be obtained

18

19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and _____9_____

20 individuals who will perform the interventions (eg, surgeons, psychotherapists)

21

22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be NA (no

23 administered diagnostic study),

24 alternative:

25 _____8_____

26

27 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose _____NA (each

28 change in response to harms, participant request, or improving/worsening disease) patient will be

29 assessed by both

30 diagnostic

31 approaches),

32 alternative:

33 _____8_____

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1		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____NA (no intervention, routine care), alternative: _____16_____
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7		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____10_____
8				
9	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____9,10_____
10				
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15	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____10,11,12_____
16				
17				
18	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9,10_____
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21	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____12,13_____
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Methods: Assignment of interventions (for controlled trials)

Allocation:

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28	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____NA_____
29				
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34	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____NA_____
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38	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____
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1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____7,11,16_
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3				
4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____16_____
5				
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7				

8 **Methods: Data collection, management, and analysis**

9				
10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13,14_
11				
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA (no interventions)_
16				
17				
18				

19	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____13,14, 15_
20				
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____9,10_
24				
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27		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
28				
29				
30				

31		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____NA_____
32				

32 **Methods: Monitoring**

33				
34	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
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40		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
41				
42				

1	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_____15_____
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3				
4	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_____15,16_____
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8	Ethics and dissemination			
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10	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_____16, 18, 19, Additional file 3_____
11				
12				
13				
14	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_____19_____
15				
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17				
18	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	_____12,13_____
19				
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21				
22		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	_____NA_____
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24				
25	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	_____13,15_____
26				
27				
28	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_____18_____
29				
30				
31	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	_____18_____
32				
33				
34	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	_____NA_____
35				
36				
37				
38	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_____11,16_____
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31b	Authorship eligibility guidelines and any intended use of professional writers	_____18_____
31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
Appendices		
Informed consent materials	32 Model consent form and other related documentation given to participants and authorised surrogates	_____Additional file 2_____
Biological specimens	33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_____NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.

Patient Information (Parents)

Dear parents,

we would like to include your child in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

Your child was or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. Due to necessary monitoring and therapy we will gather laboratory results and vital signs continually.

During the clinical trial these laboratory and monitoring details will be analyzed with regard to a pronounced, generalized inflammatory reaction (Systemic inflammatory response syndrome (SIRS)) using the support of a computer-based system. The objective is to support the doctors in early recognition of SIRS.

The recognition of SIRS on a PICU is a complex task that is quite suitable for a Clinical Decision-Support System. SIRS is caused by different reasons, for example surgery, injuries or infection. It is a typical occurrence at PICU-patients and puts the patient under additional strain independent from the original reason for admittance. For diagnosing SIRS in paediatric patients correctly we have to find abnormalities in different vital signs and laboratory results which have age related reference values, making it an advanced task.

The development and clinical trial of a CDSS for SIRS in paediatric patients is the result of a cooperation between the Department of Paediatric Cardiology and Intensive Care Medicine of Medizinische Hochschule Hannover and the Peter L. Reichertz Institut für

1
2
3 Medizinische Informatik der Technischen Universität Braunschweig und der
4 Medizinischen Hochschule Hannover (PLRI).
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8 **Are there any risks by taking part in the clinical trial?**
9

10 The CDSS will only analyze data that is taken and saved during your child's admittance
11 on the PICU anyway. There won't be any additional blood tests, monitoring or
12 examinations. These standardized raised data will be saved in a pseudonymized way
13 that ensures the patient's privacy.
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18 **What happens if I don't agree to take part in the clinical trial?**
19

20 The whole team will respect your decision if you do not want your child to take part in
21 the clinical trial. This will not be evaluated or have any negative effect on your child's
22 treatment. You can also revoke your agreement anytime.
23
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27 **Privacy Policy**
28

29 The data raised and saved for the trial are pseudonymized and it is impossible to
30 reconnect them to an individual. The data will be saved for 10 years and deleted
31 afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.
32
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38 I received the information and consent to the clinical trial mentioned above.
39

40 Yes

No
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48 _____
49 (Date and signature of the parent/legal guardian)
50
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56 _____
57 (Date and signature of the medical doctor)
58
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60

Patient Information (Patient)

Dear patient,

we would like to include you in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

You were or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. To treat you best we will monitor your vital signs as heartbeat, blood pressure and respiratory rate and take blood tests to monitor your white blood count and other inflammatory parameters. The results will be saved.

We know about the occurrence of extreme inflammatory reactions in paediatric patients. These can be caused by several reasons as surgery, injury or infection. We can measure these by changes in your vital signs, temperature or white blood count.

With a clinical trial something new is tested, for example some treatment. For this clinical trial your monitoring or vital sign data will be analyzed by a computer programme to support your doctors to detect changes that might be caused by an inflammatory reaction as soon as possible. The sooner we are aware we can adjust your treatment.

Are there any risks by taking part in the clinical trial?

The CDSS will only analyze data that is taken and saved during your admittance on the PICU anyway. There won't be any additional blood tests, monitoring or examinations. These standardized raised data will be saved in a pseudonymized way that ensures the patient's privacy.

What happens if I don't agree to take part in the clinical trial?

The whole team will respect your decision if you do not want to take part in the clinical trial. This will not be evaluated or have any negative effect on your treatment. You can also revoke your agreement anytime.

Privacy Policy

The data raised and saved for the trial are pseudonymized and it is impossible to reconnect them to an individual. The data will be saved for 10 years and deleted afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.

I received the information and consent to the clinical trial mentioned above.

Yes

No

(Date and signature of the patient)

(Date and signature of the medical doctor)



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Hannover**

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OE 6730 – im Hause

Nr. 7804_BO_S_2018

Evaluation der diagnostischen Genauigkeit eines Clinical Decision-Support Systems (CDSS) zur Unterstützung der Erkennung von SIRS und Sepsis auf der pädiatrischen Intensivstation im Vergleich zu medizinischem Fachpersonal

Sehr geehrter Herr Kollege Jack,

die Mitglieder der Ethikkommission haben auf ihrer Sitzung am 21.03.2018 über o.g. Antrag beraten. Nach Eingang der gemäß unserem Schreiben vom 26.03.2018 überarbeiteten Unterlagen bestehen keine Bedenken gegenüber der Durchführung der Studie.

Die Ethikkommission weist darauf hin, dass die ärztliche und juristische Verantwortung bei den jeweiligen Prüfärzten verbleibt.

Datenschutzrechtliche Aspekte von Forschungsvorhaben werden durch die Ethikkommission grundsätzlich nur cursorisch geprüft. Dieses Votum / diese Bewertung ersetzt mithin nicht die Konsultation des zuständigen Datenschutzbeauftragten.

Mit besten Grüßen

Prof. Dr. Stefan Engeli
Vorsitzender der Ethikkommission

Nr. 7804_BO_S_2018

Folgende Mitglieder haben an der Beratung des o.g. Antrages mitgewirkt:

Prof. Dr. St. Engeli (Vorsitzender), Klinische Pharmakologie der MHH

PD Dr. U.-V. Albrecht, Stellv. Leiter des Peter L. Reichertz Institut für Medizinische Informatik

Prof. Dr. A. M. Das, Leiter der Pädiatrischen Stoffwechselmedizin, Klinik für Päd. Nieren-, Leber- und Stoffwechselerkrankungen, Zentrum Kinderheilkunde und Jugendmedizin der MHH

Dr. J. Graubner, Arzt für Allgemeinmedizin

Prof. Dr. Thomas Illig, Leiter Biobank (HUB)

Prof. Dr. A. Koch, Leiter der Abt. Biometrie der MHH

Frau Prof. Dr. B. Lohff, Em. Leiterin der Abt. Geschichte, Ethik und Philosophie der Medizin der MHH

Dr. Oliver Pramann, Fachanwalt für Medizinrecht

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Prof. Dr. Peter Vogt, Leiter der Klinik für Plastische und Wiederherstellungschirurgie, MHH

BMJ Open

CADDIE2 - Evaluation of a clinical decision-support system for early detection of systemic inflammatory response syndrome in pediatric intensive care: study protocol for a diagnostic study

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Health informatics, Intensive care, Infectious diseases, Diagnostics
Keywords:	Clinical Decision Support Systems, Clinical Trial, Systemic Inflammatory Response Syndrome, Paediatric intensive & critical care < INTENSIVE & CRITICAL CARE

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1 CADDIE2 - Evaluation of a clinical decision-support system for early 2 detection of systemic inflammatory response syndrome in pediatric 3 intensive care: study protocol for a diagnostic study

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38 ABSTRACT

39 **Introduction:** Systemic inflammatory response syndrome (SIRS) is one of the most critical
40 indicators determining the clinical outcome of pediatric intensive care patients. Clinical
41 decision-support systems (CDSS) can be designed to support clinicians in detection and
42 treatment. However, the use of such systems is highly discussed as they are often associated
43 with accuracy problems and “alert fatigue”. We designed a CDSS for detection of pediatric
44 SIRS and hypothesize that a high diagnostic accuracy together with an adequate alerting will
45 accelerate the use. Our study will (1) determine the diagnostic accuracy of the CDSS
46 compared to gold standard decisions created by two, blinded experienced pediatricians, and
47 (2) compare the system’s diagnostic accuracy with that of routine clinical care decisions
48 compared to the same gold standard.

49 **Methods and analysis:** CADDIE2 is a prospective diagnostic accuracy study taking place at
50 the Department of Pediatric Cardiology and Intensive Care Medicine at the Hannover Medical
51 School; it represents the second step towards our vision of cross-institutional and data-driven
52 decision support for intensive care environments (CADDIE). The study comprises (1)
53 recruitment of up to 300 patients (started *August 1, 2018*), (2) creation of gold standard
54 decisions (start date *May 1, 2019*), (3) routine SIRS assessments by physicians (started with
55 recruitment), (4) SIRS assessments by a CDSS (start date *May 1, 2019*), and (5) statistical
56 analysis with a modified approach for determining sensitivity and specificity and comparing
57 the accuracy results of the different diagnostic approaches (planned start date *July 1, 2019*).

58 **Ethics and dissemination:** Ethics approval was obtained at the study center (Ethics
59 Committee of Hannover Medical School). Results of the main study will be communicated
60 via publication in a peer-reviewed journal.

61 **Trial registration:** ClinicalTrials.gov NCT03661450. Registered 07 September 2018.
62 Recruitment started August 1st, 2018, and it is expected to continue until May 2019.

63 **Protocol version:** V1.0, 2018-Mar-06 Original

64 **Keywords:** Clinical Decision Support Systems, Clinical Trial, Paediatric intensive & critical
65 care, Systemic Inflammatory Response Syndrome

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3 66 **Abbreviations:** CADDIE, Cross-institutional and Data-driven Decision Support for Intensive
4 Care Environments; CDSS, Clinical Decision-Support System; GCP, Good Clinical Practice;
5 67
6 68 GMDS, German Association for Medical Informatics, Biometry and Epidemiology; ICD,
7 International Statistical Classification of Diseases and Related Health Problems; IPSCC,
8 69 International Pediatric Sepsis Consensus Conference; PICU, Pediatric Intensive Care Unit;
9 70
10 71 PDMS, Patient Data Management System; RCT, Randomized Controlled Trials; SIRS,
11 Systemic Inflammatory Response Syndrome; STARD, Standards for Reporting Diagnostic
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13 73 Accuracy Studies; SPIRIT, Standard Protocol Items: Recommendations for Interventional
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17 Trials.
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For peer review only

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3 75 **ARTICLE SUMMARY**
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5 76 **Strengths and limitations of this study**
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- 7 77
8 78 • Related studies reached successful results in the context of clinical decision-support
9 79 systems (CDSS) for SIRS detection, but due to the study design, the reported results often
10 80 do not reflect the usefulness of such systems in routine clinical care.
11
12 81 • We present an adjusted and novel approach for the design and the statistical analysis of
13 82 diagnostic studies for CDSSs from a more routine clinical care perspective, because our
14 83 study comprises
15
16 84 • (1) the validation of the clinical decision-support system in comparison to the assessment
17 85 of two experienced clinicians by blinded chart review (gold standard) and
18
19 86 • (2) the comparison of the system's diagnostic accuracy with the diagnostic accuracy of
20 87 real-time assessments by clinicians working in routine clinical care and manually
21 88 evaluating patients.
22
23 89 • Although our study does not comprise specific evaluations of CDSS user acceptance, it is
24 90 suited to present the potentials of CDSS use in routine clinical care and, thus, to foster the
25 91 willingness to trust the system in future.
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93 INTRODUCTION

94 The first definition of systemic inflammatory response syndrome (SIRS) and sepsis was made
95 by the members of the “American College of Chest Physicians/Society of Critical Care
96 Medicine Consensus Conference Committee” in 1992. SIRS was described as a “systemic
97 inflammatory response to a variety of severe clinical insults”, sepsis on the other hand was
98 “the systemic response to infection” [1]. The criteria have been adapted to pediatric patients
99 by the International Pediatric Sepsis Consensus Conference (IPSCC) in 2005 [2]. According
100 to this, SIRS was present if the patient presented two or more of the defined age-dependent
101 criteria (at least an abnormal core temperature or leukocyte count). The other criteria include
102 abnormal heart rate and respiratory rate. According to the IPSCC, sepsis is defined as SIRS in
103 the presence of or as a result of suspected or proven infection. Although the definition of
104 SIRS is no longer taken into account for the sepsis diagnosis in adult medicine, it is still
105 relevant in pediatric medicine. Pediatric patients with SIRS and sepsis are known to have a
106 higher risk of morbidity and mortality [3-6]. SIRS in pediatric patients also causes a
107 significantly prolonged stay in intensive care after cardiothoracic surgery [7] and entails an
108 increased probability of organ dysfunctions [8].

109 Independent of the underlying disease and together with SIRS and sepsis, organ dysfunction
110 and failure represent the critical determinants of patient outcome in both adult and pediatric
111 medicine. Prevention and rapid effective treatment of multi-organ dysfunction and failure is
112 crucial for survival. An optimization of the diagnostic and therapeutic workflow is likely to
113 have an immense impact on clinical outcome of critically-ill patients. In pediatric septic shock
114 patients, every hour without appropriate treatment was associated with an increased chance of
115 death by 40% [9]. Conclusively, early recognition and treatment of pediatric SIRS and sepsis
116 are vital [10].

117 To assure that patients are treated with the best available approaches, evidence-based
118 medicine [11] together with personal expertise represent the current *gold standard* of medical
119 patient management. However, clinicians are often confronted with a stressful environment,
120 which fosters decision-making with a lower quality than aspired [12]. This is particularly true
121 for pediatric intensive care units (PICU), in which clinicians work under challenging
122 conditions characterized by a high degree of dynamics, uncertainty and risk, time pressure and
123 a vast amount of data. Altogether, these factors carry risk for medical errors and adverse
124 effects on patient safety [13-15].

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3 125 To tackle these challenges, clinicians can be supported by clinical decision-support systems
4 (CDSS). The growing digitalization in medicine involves an immense amount of highly
5 126 (CDSS). The growing digitalization in medicine involves an immense amount of highly
6 heterogeneous datasets carrying the potential to be valuable for other purposes than initially
7 127 heterogeneous datasets carrying the potential to be valuable for other purposes than initially
8 expected (*secondary use of data*); the design of systems that are able to efficiently reuse and
9 128 expected (*secondary use of data*); the design of systems that are able to efficiently reuse and
10 assimilate routine data, and thereby making data meaningful for clinical care, is fostered.
11 129 assimilate routine data, and thereby making data meaningful for clinical care, is fostered.
12 CDSS are shining examples for systems processing clinical and non-clinical data and
13 130 CDSS are shining examples for systems processing clinical and non-clinical data and
14 delivering an added value by detecting diseases, recommending therapies or uncovering yet
15 131 delivering an added value by detecting diseases, recommending therapies or uncovering yet
16 unknown disease patterns [16]. Particularly in sophisticated intensive care settings, the use of
17 132 unknown disease patterns [16]. Particularly in sophisticated intensive care settings, the use of
18 highly developed patient data management systems (PDMS) allow the continuous recording
19 133 highly developed patient data management systems (PDMS) allow the continuous recording
20 of multiple clinical parameters and make high quality data available.
21 134 of multiple clinical parameters and make high quality data available.

22 135 In our previous work, we designed a rule-based and interoperable CDSS for the detection of
23 136 SIRS in pediatric intensive care[17]. The CDSS is able to retrieve and evaluate dynamic facts
24 137 SIRS in pediatric intensive care[17]. The CDSS is able to retrieve and evaluate dynamic facts
25 as routinely and automatically measured parameters from the bedside monitors to detect SIRS
26 138 as routinely and automatically measured parameters from the bedside monitors to detect SIRS
27 episodes. However, only when used in routine clinical care, the benefits can be translated into
28 139 episodes. However, only when used in routine clinical care, the benefits can be translated into
29 clinical care. Consequently, an extensive evaluation of the system's diagnostic accuracy is
30 140 clinical care. Consequently, an extensive evaluation of the system's diagnostic accuracy is
31 needed to assure that users will trust the system. This need is even aggravated in our context,
32 141 needed to assure that users will trust the system. This need is even aggravated in our context,
33 because we strive for (1) using an automatic SIRS-labelling to train machine learning
34 142 because we strive for (1) using an automatic SIRS-labelling to train machine learning
35 algorithms, and (2) reaching a self-learning system able to continuously process data and
36 143 algorithms, and (2) reaching a self-learning system able to continuously process data and
37 optimize its algorithms when used in routine care (*Learning Healthcare System*) [18]. In our
38 144 optimize its algorithms when used in routine care (*Learning Healthcare System*) [18]. In our
39 previous work, we describe this approach for CDSS design, in which we denote the
40 145 previous work, we describe this approach for CDSS design, in which we denote the
41 conduction of such a study as **second** important step towards the vision of cross-institutional
42 146 conduction of such a study as **second** important step towards the vision of cross-institutional
43 **and data-driven decision support for intensive care environments (CADDIE2)** [18].

44 147 Related studies already reached satisfying results [19-21]. However, due to the study designs,
45 148 Related studies already reached satisfying results [19-21]. However, due to the study designs,
46 the reported results might not reflect the usefulness of the CDSS in routine clinical care.
47 149 the reported results might not reflect the usefulness of the CDSS in routine clinical care.
48 Often, the coding of diagnoses as ICD (International Statistical Classification of Diseases and
49 150 Often, the coding of diagnoses as ICD (International Statistical Classification of Diseases and
50 Related Health Problems) is used as gold standard against which the system's results are
51 151 Related Health Problems) is used as gold standard against which the system's results are
52 compared to. However, in ICD, episodes of SIRS and sepsis are not documented detailed
53 152 compared to. However, in ICD, episodes of SIRS and sepsis are not documented detailed
54 enough, e.g. the time of occurrence is not described. Even though sometimes additional scores
55 153 enough, e.g. the time of occurrence is not described. Even though sometimes additional scores
56 are used, not all relevant SIRS episodes can be reflected. Hence, systems evaluated with such
57 154 are used, not all relevant SIRS episodes can be reflected. Hence, systems evaluated with such
58 an approach in fact have been successfully trained, but with respects to the ICD
59 155 an approach in fact have been successfully trained, but with respects to the ICD
60 documentation and not routine decision-making. Additionally, the study population is often
61 156 documentation and not routine decision-making. Additionally, the study population is often
62 very preselected and requires a complete data set of all parameters required as input for the
63 157 very preselected and requires a complete data set of all parameters required as input for the
64 algorithm used. Such perfect data sets are often not available in clinical routine settings.
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3 158 The exploration of factors influencing a successful CDSS implementation is a ubiquitous
4
5 159 topic. In a recent literature review, Kilsdonk et al. [22] identified such factors for guideline-
6
7 160 based CDSS implementation. One of the aspects reported mostly deals with the *information*
8
9 161 *quality of the system* and covers the relevance of data and messages delivered by the system
10
11 162 [22]. This finding relates to a well-known and obviously still unsolved issue called “alert
12
13 163 fatigue” [23]. Other recent work published by Liberati et al. [24] describe the conduction of a
14
15 164 qualitative study to identify different clusters of attitudes and barriers towards CDSS
16
17 165 implementation. The authors describe that, together with a poor integration in the clinical
18
19 166 workflow, the “fear of experiencing excessive number of alerts” [24] is one of the factors
20
21 167 hindering the willingness to trust systems and to believe in their unforeseen opportunities
22
23 168 (*mutual adjustment*). This step is declared as one of the most challenging obstacles in CDSS
24
25 169 adoption. It is suggested to integrate and evaluate the CDSS in routine clinical care and with
26
27 170 real users to overcome these limitations [24].

28
29 171 Against the background of our CADDIE objectives and the findings on successful CDSS
30
31 172 implementations, we conclude that there is a need for a CADDIE2 trial focusing on validating
32
33 173 the CDSS for SIRS and sepsis detection in routine clinical care.

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36 175 **Study objectives and diagnostic approaches**

37 176 The **primary goal** is the evaluation of the diagnostic accuracy of the CDSS for detecting
38
39 177 SIRS in PICU patients (*diagnostic approach I*), in comparison to the assessments of two
40
41 178 clinicians by blinded chart review. In case of disagreement, a third clinician will be consulted.
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43 179 The expert assessments will be treated as gold standard and contain retrospective, extensive
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45 180 data analyses. These comprise evaluating all patients’ measurements, not restricted to the
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47 181 SIRS parameters, including additional values for vital signs validated hourly by the attending
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49 182 nurse.

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51 183 The **secondary goal** is to compare the diagnostic accuracy of the CDSS for detecting SIRS in
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53 184 PICU patients evaluated against this gold standard, to the diagnostic accuracy of routine
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55 185 assessments of different clinicians working in routine clinical care (*diagnostic approach II*)
56
57 186 when compared to the same gold standard.

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188 **Trial design and study setting**

189 The CADDIE2 study is designed as a single-arm, controlled, prospective diagnostic accuracy
190 study. Single study center is the Department of Pediatric Cardiology and Intensive Care
191 Medicine at the Hannover Medical School (monocentric). The estimated study duration is one
192 year. Our study does not contain comparisons between different patient populations (single-
193 arm) or interventions (no randomization). Each patient will be assessed by both diagnostic
194 approaches.

196 **METHODS AND ANALYSIS**

197 **Preceding studies**

198 We can take advantage of the results of a randomized controlled trial (RCT) with 807 PICU
199 patients from the same ward for the planned study. The expected SIRS prevalence on
200 admission to PICU was reported as 5/100; 20-10% of the patients developed SIRS later on
201 during their PICU stay [25]. Furthermore, we conducted a proof-of-concept study focusing on
202 the technical practicability of the CDSS, yielding at promising results for both the technical
203 infrastructure and the accuracy of the system (sensitivity of 1.00, specificity of 0.94) [17].

205 **Recommendations and guidelines**

206 We reviewed work on study planning, national recommendations and templates of ethics
207 committees and associations, and followed the Good Clinical Practice (GCP) in non-drug
208 trials. We designed our study in accordance with the “Standards for Reporting Diagnostic
209 Accuracy Studies” (STARD) [26] and the “Standard Protocol Items: Recommendations for
210 Interventional Trials (SPIRIT) [27] guidelines (see Figure 1, see additional file 1).

212 **Patient population and eligibility criteria**

213 All pediatric patients aged 0 to 18 years admitted to the study center - independent of the
214 gender, the underlying disease or the time of admission - will be asked for their consent to
215 participate. Patients will be recruited continuously and included, if a positive consent is
216 available; and their length of stay exceeds twelve hours because any patient developing SIRS
217 will not be discharged earlier.

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3 218 The physicians are specialized pediatricians with experience in pediatric intensive care. There
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5 219 are always one experienced (working in this PICU for over a year) and one less experienced
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7 220 physician (working in this PICU for less than a year) in charge. The reviewers who will
8
9 221 perform the manual chart review for creating gold standard decisions are specialized
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11 222 pediatricians and very experienced (working in this PICU for over three years), able to
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13 223 discriminate unsound and missing data.
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225 **Outcome measures**

17 226 Sensitivity and specificity *on the level of patients* will be used as primary outcome measures.
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19 227 As second outcome measure, sensitivity and specificity also can be determined *on the level of*
20
21 228 *intensive care days*.
22

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230 **Statistical analysis and sample size calculation**

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26
27 231 For the primary outcome measure, sensitivity and specificity will be determined together with
28
29 232 *Wald confidence intervals*. The comparison will be carried out by comparing the lower bound
30
31 233 of the confidence interval with the null hypothesis (which is, as described below in the sample
32
33 234 size calculation paragraph, a sensitivity of 0.90, and a specificity of 0.80). If the lower bound
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35 235 of the 95% confidence intervals for sensitivity and specificity are both above the values of the
36
37 236 pre-defined null hypotheses, we will reject the null hypotheses. For the secondary outcome
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39 237 measure, sensitivity and specificity will be determined together with confidence intervals
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41 238 based on *general estimating equations*. Additionally, for the secondary goal of comparing the
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43 239 diagnostic accuracy of the CDSS to the one of routine decisions (both when evaluated against
44
45 240 the gold standard), sensitivity and specificity values will be compared by means of *McNemar*
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47 241 *tests* and confidence intervals constructed based on *general estimating equations*.

46 242 All analyses will be accompanied by secondary subgroup analyses, stratified e.g. by patients'
47
48 243 age, type of shift and clinical picture associated with SIRS detection (including SIRS, sepsis,
49
50 244 severe sepsis and septic shock). Factors that might modify the diagnostic accuracy of the
51
52 245 CDSS will thus be evaluated in an exploratory way, allowing a better understanding of
53
54 246 potential limitations of the system. SIRS prevalence and incidence will be monitored
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56 247 throughout the pilot phase and the main phase of the study, and will be compared to pre-study
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58 248 values in order to estimate the risk of a training effect on physicians' real-time diagnoses
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60 249 caused by knowledge about the aims of this study.

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3 250 For analyzing the primary outcome measure, the assessment is carried out on the patient level.
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5 251 This is challenging since the assessment is not cross-sectional (as e.g. if the unit of assessment
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7 252 would be an hour respectively a shift) but needs to incorporate the complex longitudinal
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9 253 course of potential assessments within one patient. It is, however, the clinically most
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11 254 meaningful and the most conservative approach for estimating the diagnostic accuracy if
12
13 255 conducted correctly. In our case, the entire period of stay is considered and information are
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15 256 aggregated on the patient level. Every person contributes (given that a correct diagnosis is
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17 257 restricted to the period of an hour respectively a shift) parts of its period of stay to the
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19 258 calculation of specificity independently of if the gold standard recorded a SIRS at some point
20
21 259 since everybody will have periods without SIRS diagnosis (which need to be classified as
22
23 260 well correctly by the CDSS). This leads to situations, which cannot be represented in only one
24
25 261 cell of a contingency table. The classical four cases are amended by a new case, which occurs
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27 262 because the CDSS should assess the occurrence of a SIRS event with a correct timing (e.g.
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29 263 SIRS event is identified within the correct hour respectively shift). For example, this fifth case
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31 264 prevents that alert firings on day 30 of the intensive care stay will be evaluated as *true*
32
33 265 *positives* if the gold standard reports a SIRS episode on day 2. Here, the CDSS did not
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35 266 identify the SIRS episode within the correct timing. Thus, this case is used for the
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37 267 determination of both *false positives* (day 30, contributing to specificity) and *false negatives*
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39 268 (day 2, contributing to sensitivity). Hence, the fifth case (false positive and false negative) can
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41 269 be defined as follows: *the gold standard reports at least one SIRS episode, and the CDSS*
42
43 270 *detect SIRS episodes but (at least one) not within the same hour respectively shift.* All other
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45 271 cases are defined as usual (e.g. false positive: *the gold standard reports no SIRS episode but*
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47 272 *the CDSS detects one or multiple SIRS episodes).*

43 273 Based on the different cases, the sensitivity and the specificity will be determined
44
45 274 independently. For sample size calculation, the results of the proof-of-concept study were
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47 275 used as a basis (sensitivity 1.00 and specificity 0.94, when calculating on the level of days).
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49 276 For this study with the modified statistical analysis approach, a sensitivity of 90% (alternative
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51 277 hypothesis: 0.98, null hypothesis: 0.90) and a specificity of 80% (alternative hypothesis: 0.90,
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53 278 null hypothesis: 0.80) were chosen as a clinically relevant diagnostic accuracy, with a given
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55 279 accuracy of estimate of 95% (type I error = 0.05) and a power of 90% (chi square test).
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57 280 Consequently, 97 patients suffering from at least one SIRS episode (for the estimation of
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59 281 sensitivity) as well as 137 patients with or without SIRS episodes are required (for the
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3 282 estimation of specificity). Based on the expected incidence and prevalence, at least 300
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5 283 patients need to be considered.
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8 9 285 **Timeline**

10 286 Before study start, the clinicians were introduced in their tasks. No interventions, treatments
11 287 or other care-related actions are prohibited and patients are treated with standard procedures
12 288 (including data collection and measurements). Personal briefings on the routine
13 289 documentation were carried out during this *pilot phase* (July 1, 2018, duration: 1 month, see
14 290 Figure 1). A designated physician will present the study to the patients, their parents or their
15 291 legal guardians and ask for consent within the *recruiting phase* (August 1, 2018, estimated
16 292 duration: 10 months). Simultaneously, clinicians reported their findings during their working
17 293 shift per patient (routine assessments, *diagnostic approach II*). The clinicians do not perform
18 294 extensive analyses of documentations or reported data (*assessment phase I*, August 1, 2018,
19 295 estimated duration: 10 months). In the routine assessments it is documented whether the
20 296 patient suffered from SIRS, sepsis or organ dysfunction (via digital documentation form, see
21 297 Figure 2). The first two weeks of this phase will be treated as test phase.

22 298 Later on, two experienced clinicians started with their weekly, extensive, blinded review and
23 299 the definition of gold standard assessments per patient and per hour (*assessment phase II*,
24 300 May 1, 2019, estimated duration: 2 months). As soon as 97 patients suffering from one or
25 301 more SIRS episodes as well as 137 patients with one or without SIRS episodes have been
26 302 identified, the recruitment will be terminated. Simultaneously, the data sets from all recruited
27 303 patients will be integrated into a data repository to make them accessible for the CDSS. The
28 304 CDSS assessments per patients and per hour will start (*diagnostic approach I*). In the final
29 305 *analysis phase* (July 1, 2019, estimated duration: 2 months), the diagnostic accuracy of the
30 306 CDSS will be evaluated by comparing the assessments to the gold standard decisions from the
31 307 experts (primary goal of the study). Additionally, the diagnostic accuracy of the routine
32 308 assessments will be determined by comparing them to the same gold standard decisions. The
33 309 different accuracies can be compared (secondary goal of the study). Finally, the study results
34 310 will be communicated via publication in a peer-reviewed journal.
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312 **Recruitment and consent**

313 Eligible patients, their parents or their legal guardians will receive an information letter and a
314 consent form (available in German, English, Turkish and Arabic) during a personal discussion
315 with a physician. Additional information sheets for younger patients are available, one for
316 children aged six to eleven and one for children aged 12 to 18. The families will receive
317 privacy statement forms (data protection, accessibility and confidentiality; see additional file
318 2).

319

320 **Patient and public involvement**

321 There were no funds or time allocated for patient and public involvement so we were unable
322 to involve patients. We intend to disseminate the results to the participants and will invite
323 patients to help us developing an appropriate method of dissemination.

324

325 **Data management and collection**

326 The CDSS is an application with interfaces to a data repository, which is based on an
327 semantic interoperability standard for clinical information representation (*openEHR* [28]). For
328 more information, we refer to [17]. For the routine assessment (assessment phase I, diagnostic
329 approach II), we created a documentation form, which is based on the same interoperability
330 standard and the same interfaces to the data repository (see Figure 2). Thereby, all results
331 (gold standard, diagnostic approach I “CDSS”, diagnostic approach II “routine assessments”)
332 will be available in the same format. Patient data (identification, birthdate), intensive care
333 parameters (heart rate, respiratory rate, body temperature, leukocytes, neutrophils, mechanical
334 ventilation, cooling devices, pacemaker), alert parameters (SIRS, sepsis, organ dysfunction
335 with duration, beginning and end of the episode and shift), and general documentations of the
336 patient conditions, events or unintended effects will be documented and processed.

337

338

339 **Data monitoring and auditing**

340 Quality assurance measures are continuously carried out. Plausibility checks will be executed
341 while integrating data into our repository (e.g. simple counts to can uncover whether data
342 from the primary source is missing in the repository). Furthermore, the data set will be
343 reviewed by physicians with respect to randomly selected observations to guarantee the

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3 344 plausibility from a clinical perspective. By following the openEHR standard, we are able to
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5 345 automatically execute validation checks to uncover missing or wrong values when integrating
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7 346 the data sets or filling out the documentation form (e.g. definition of ranges for specific
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9 347 values, or double data entries). The study procedures will be monitored by the authors as well
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11 348 as by designated physicians and nurses. They will supervise the adherence to the study
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13 349 protocol, the procedures for routine documentation and data integration, data quality and
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15 350 privacy.

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17 352 **Data protection: data access and confidentiality**

19 353 We designed a data protection concept in cooperation with the local data security officer. The
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21 354 concept defines pseudonymization and data access procedures, outlines the patient consent,
22
23 355 and explains technical security mechanisms. All data sets collected or created as part of this
24
25 356 study are treated as strictly confidential. The data sets will be stored pseudonymized and in
26
27 357 secure conditions in the data repository located in the network of the Hannover Medical
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29 358 School. To prevent unauthorized disclosure of patient information, it is only accessible for the
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31 359 physicians and employees in charge of this study. Collected data from patients withdrawing
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33 360 their consent (drop outs), will be completely deleted from the data repository. All study files,
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35 361 the final study data sets as well as the study results will be archived for ten years in an
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37 362 approved long-term repository and in accordance to the relevant legal and statutory
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39 363 requirements. The patient will be informed about these procedures as well as their rights
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41 364 (including the possibility to withdraw the consent and to obtain information about collected
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43 365 data sets at any time), and will be asked to consent to these.

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44 367 **Ethics and dissemination**

46 368 Ethics approval was given by the Ethics Committee of Hannover Medical School (approval
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48 369 number 7804_BO_S_2018). The trial is registered with ClinicalTrials.gov (NCT03661450).
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50 370 Protocol modifications will require a formal amendment to the protocol which will be
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52 371 reported to the Hannover Medical School Ethics Committee for approval. All aspects are
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54 372 designed according to the General Data Protection Regulation from the European Union
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56 373 (2016/679) and are accepted by the data security officer of the Hannover Medical School.
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58 374 Further details on data protection aspects can be requested from the authors. Consent to
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60 375 participate will be given by the patients, by their parents or by their legal guardians by signing

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3 376 a study consent form. Results of the main study will be communicated via publication in a
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5 377 peer-reviewed journal. We intend to disseminate the results to the participants through an
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7 378 appropriate method of dissemination to be defined.
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10 380 **DISCUSSION**

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13 381 To be used in the long run, CDSSs have to deliver relevant information in a timely manner
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15 382 and at an adequate frequency. Current approaches for evaluating the usefulness of CDSS
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17 383 indeed present positive results. However, due to a restricted study design not designed
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19 384 towards daily work conditions, results may not represent the system feasibility in routine
20
21 385 clinical care. With our work, we contribute a modified study design for evaluating the
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23 386 diagnostic accuracy of a CDSS with a strong focus on routine clinical care. We hypothesize
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25 387 that such an evaluation will demonstrate the potentials of CDSS use in routine clinical care. In
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27 388 case of a positive study outcome, we will be able to reason that our CDSS is not only feasible
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29 389 from a technical but also from a clinical perspective as it supports clinicians in critical
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31 390 diagnostic decision-making. For evaluation, a so-called gold standard representing the true
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33 391 state of the patient is required. However, in complex, knowledge-and experience-based
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35 392 contexts as diagnostic decision-making, reproducible, objective and quantitative “gold
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37 393 standards” are rare. We use an excessive evaluation of the patient data by two experience
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39 394 clinicians as benchmark. To reduce possible biases, the clinicians are blinded to each other
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41 395 and to the CDSS. In situations of disagreement, a third clinician will be consulted, decisions
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43 396 will be revealed and a consensus decision will be reported. We are aware that our approach is
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45 397 time-consuming requiring highly engaged clinicians. Because of the stressful PICU
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47 398 environment, assessments may be delayed, and thus, the study timeline may not be adhered.
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49 399 For an early recognition of issues and study monitoring at the ward, an assistant physician is
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51 400 in charge. Also the routine assessments of clinicians have to be managed as they are at the
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53 401 same risk to be biased. Clinical documentation might be handled more meticulous at the
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55 402 beginning and more careless in the end of the study. To prevent the latter, the new
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57 403 documentation form was designed in cooperation with the users and integrated in the PDMS
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59 404 used daily. Together with the designated study monitor, this integration raised the satisfactory
60
405 and the utilization rate of the form as well as the adherence to the study protocol.
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407 For sample size calculation, it might be possible that the incidence was overestimated, so that
in our settings more than 300 patients are needed to reach 97 patients suffering from at least

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3 408 one SIRS episode. The recruitment will be continuously aligned towards the number of
4
5 409 recruited SIRS patients to be able to stop the recruitment as soon as the required number has
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7 410 been reached. Our expected values for sensitivity and specificity are rather conservative
8
9 411 because we decided to primarily use an equally conservative statistical analysis approach.
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11 412 However, the expected values are treated as acceptable in clinical routine as the diagnostic
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13 413 accuracy of the system will be over a critical minimum (and with respect to the aspired
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15 414 second goal of our study, even better than in clinical routine decision-making). At the same
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17 415 time, alert fatigue will be prevented because specificity is equally high. We are confident that
18
19 416 our thoughts meet the need for an optimum balance between sensitivity and specificity, e.g. as
20
21 417 reported by Coleman et al. [23]. Nevertheless, we will enhance our results with a more liberal
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23 418 analysis on the level of days.

24
25 419 Our study has been successfully started with recruitment according to this design and
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27 420 promises valuable results. When reaching a good diagnostic accuracy compared to the gold
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29 421 standard as well as advantages over the diagnostic accuracy of routine assessments, we are
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31 422 optimistic that our users are willing to trust and use the system in future. Moreover, this will
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33 423 allow the conduction of future studies as for example the evaluation of patient outcomes, user
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35 424 acceptability, or real-time performance of the system.
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436 STATEMENTS

437 Author Contributions

438 AW was responsible for design and implementation of the presented clinical decision-support
439 system and the outline of the study protocol, and has drafted the manuscript. TJ provided
440 clinical expertise for the use case and the design of the underlying knowledge model, leded
441 the proof-of-concept study and co-drafted the manuscript. AK was primarily responsible for
442 the design of the statistical analysis, the sample size calculation and the authoring of the
443 corresponding sections. BS and SM helped in the conception of the general study approach
444 but especially for definition of goals and outcome measures, timing and patient recruitment;
445 SM is responsible for patient recruitment and monitors the study at the ward. PB and MM
446 provided clinical expertise for study design, revised the manuscript critically, and gave
447 subject-specific advices as well as the final approval of the manuscript version to be
448 published. All authors read and approved the final manuscript.

449 Competing interests

450 The authors declare that they have no competing interests.

451 Funding

452 No funding to declare.

453 Availability of data and material

454 The datasets generated and/or analyzed during the current study are not publicly available due
455 to data privacy and security matters of patients but are available from the corresponding
456 author on reasonable request.

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459 Systems of the Hannover Medical School for supporting in matters of data access and
460 integration.

461 **REFERENCES**

- 462 1 American College of Chest Physicians/Society of Critical Care Medicine Consensus
463 Conference: definitions for sepsis and organ failure and guidelines for the use of
464 innovative therapies in sepsis. *Crit Care Med* 1992;20(6):864–74. PubMed PMID:
465 1597042.
- 466 2 Goldstein B, Giroir B, Randolph A. International pediatric sepsis consensus conference:
467 Definitions for sepsis and organ dysfunction in pediatrics*. *Pediatr Crit Care Med*
468 2005;6(1):2–8. doi: 10.1097/01.PCC.0000149131.72248.E6.
- 469 3 Wolfler A, Silvani P, Musicco M, et al. Incidence of and mortality due to sepsis, severe
470 sepsis and septic shock in Italian Pediatric Intensive Care Units: A prospective national
471 survey. *Intensive Care Med* 2008;34(9):1690–97. doi: 10.1007/s00134-008-1148-y.
- 472 4 Cvetkovic M, Lutman D, Ramnarayan P, et al. Timing of death in children referred for
473 intensive care with severe sepsis: Implications for interventional studies. *Pediatric*
474 *Critical Care Medicine* 2015;16(5):410–17. doi: 10.1097/PCC.0000000000000385.
- 475 5 Creedon JK, Vargas S, Asaro LA, et al. Timing of Antibiotic Administration in Pediatric
476 Sepsis. *Pediatr Emerg Care* 2018. doi: 10.1097/PEC.0000000000001663.
- 477 6 Kortz TB, Sawe HR, Murray B, et al. Clinical Presentation and Outcomes among
478 Children with Sepsis Presenting to a Public Tertiary Hospital in Tanzania. *Front Pediatr*
479 2017;5:278. doi: 10.3389/fped.2017.00278.
- 480 7 Boehne M, Sasse M, Karch A, et al. Systemic inflammatory response syndrome after
481 pediatric congenital heart surgery: Incidence, risk factors, and clinical outcome. *J Card*
482 *Surg* 2017;32(2):116–25. doi: 10.1111/jocs.12879.
- 483 8 Ganjoo S, Ahmad K, Qureshi UA, et al. Clinical Epidemiology of SIRS and Sepsis in
484 Newly Admitted Children. *Indian J Pediatr* 2015;82(8):698–702. doi: 10.1007/s12098-
485 014-1618-x.
- 486 9 Han YY, Carcillo JA, Dragotta MA, et al. Early reversal of pediatric-neonatal septic
487 shock by community physicians is associated with improved outcome. *Pediatrics*
488 2003;112(4):793–99. doi: 10.1542/peds.112.4.793.
- 489 10 Paul R. Recognition, Diagnostics, and Management of Pediatric Severe Sepsis and
490 Septic Shock in the Emergency Department. *Pediatr Clin North Am* 2018;65(6):1107–
491 18. doi: 10.1016/j.pcl.2018.07.012.
- 492 11 Sackett DL. Evidence-based medicine. *Semin Perinatol* 1997;21(1):3–5. doi: 10.1016/
493 S0146-0005(97)80013-4.

- 1
2
3 494 12 Zavala AM, Day GE, Plummer D, et al. Decision-making under pressure: Medical errors
4 in uncertain and dynamic environments. *Aust Health Rev* 2017. doi: 10.1071/AH16088.
5 495
6 496 13 Lighthall GK, Vazquez-Guillamet C. Understanding Decision Making in Critical Care.
7 *Clin Med Res* 2015;13(3-4):156–68. doi: 10.3121/cmr.2015.1289.
8 497
9 498 14 Castaneda C, Nalley K, Mannion C, et al. Clinical decision support systems for
10 improving diagnostic accuracy and achieving precision medicine. *J Clin Bioinforma*
11 499
12 500 2015;5:4. doi: 10.1186/s13336-015-0019-3.
13
14 501 15 Lincoln P, Manning M-J, Hamilton S, et al. A pediatric critical care practice group: use
15 of expertise and evidence-based practice in identifying and establishing "best" practice.
16 502
17 503 *Crit Care Nurse* 2013;33(2):85–87. doi: 10.4037/ccn2013740.
18
19 504 16 Shortliffe EH. Biomedical Informatics: Defining the Science and Its Role in Health
20 Professional Education. In: Hutchison D, Kanade T, Kittler J, et al., eds. Information
21 505
22 506 Quality in e-Health. Berlin, Heidelberg: Springer Berlin Heidelberg 2011:711–14.
23
24 507 17 Wulff A, Haarbrandt B, Tute E, et al. An interoperable clinical decision-support system
25 for early detection of SIRS in pediatric intensive care using openEHR. *Artif Intell Med*
26 508
27 509 2018;89:10–23. doi: 10.1016/j.artmed.2018.04.012.
28
29 510 18 Wulff A, Marschollek M. Learning Healthcare Systems in Pediatrics: Cross-Institutional
30 and Data-Driven Decision-Support for Intensive Care Environments (CADDIE). *Stud*
31 511
32 512 *Health Technol Inform* 2018;251:109–12. doi:10.3233/978-1-61499-880-8-109
33
34 513 19 Faisal M, Scally A, Richardson D, et al. Development and External Validation of an
35 Automated Computer-Aided Risk Score for Predicting Sepsis in Emergency Medical
36 514
37 515 Admissions Using the Patient's First Electronically Recorded Vital Signs and Blood Test
38 Results. *Crit Care Med* 2018;46(4):612–18. doi: 10.1097/CCM.0000000000002967.
39 516
40 517 20 Austrian JS, Jamin CT, Doty GR, et al. Impact of an emergency department electronic
41 sepsis surveillance system on patient mortality and length of stay. *J Am Med Inform*
42 518
43 519 *Assoc* 2018;25(5):523–29. doi: 10.1093/jamia/ocx072.
44
45 520 21 Mao Q, Jay M, Hoffman JL, et al. Multicentre validation of a sepsis prediction algorithm
46 using only vital sign data in the emergency department, general ward and ICU. *BMJ*
47 521
48 522 *Open* 2018;8(1):e017833. doi: 10.1136/bmjopen-2017-017833.
49
50 523 22 Kilsdonk E, Peute LW, Jaspers MW. Factors influencing implementation success of
51 guideline-based clinical decision support systems: A systematic review and gaps
52 524
53 525 analysis. *Int J Med Inform* 2017;98:56–64. doi: 10.1016/j.ijmedinf.2016.12.001.
54
55
56
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59
60

- 1
2
3 526 23 Coleman JJ, van der Sijs H, Haefeli WE, et al. On the alert: Future priorities for alerts in
4 clinical decision support for computerized physician order entry identified from a
5 527 European workshop. *BMC Med Inform Decis Mak* 2013;13:111. doi: 10.1186/1472-
6 528 6947-13-111.
7
8 529
9
10 530 24 Liberati EG, Ruggiero F, Galuppo L, et al. What hinders the uptake of computerized
11 decision support systems in hospitals? A qualitative study and framework for
12 531 implementation. *Implement Sci* 2017;12(1):113. doi: 10.1186/s13012-017-0644-2.
13 532
14
15 533 25 Jack T, Boehne M, Brent BE, et al. In-line filtration reduces severe complications and
16 length of stay on pediatric intensive care unit: A prospective, randomized, controlled
17 534 trial. *Intensive Care Med* 2012;38(6):1008–16. doi: 10.1007/s00134-012-2539-7.
18 535
19
20 536 26 Cohen JF, Korevaar DA, Altman DG, et al. STARD 2015 guidelines for reporting
21 diagnostic accuracy studies: Explanation and elaboration. *BMJ Open*
22 537 2016;6(11):e012799. doi: 10.1136/bmjopen-2016-012799.
23 538
24
25 539 27 Chan A-W, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration:
26 Guidance for protocols of clinical trials. *BMJ* 2013;346:e7586. doi: 10.1136/bmj.e7586.
27 540
28
29 541 28 Thomas Beale. Archetypes: Constraint-based Domain Models for Future-proof
30 Information Systems. In: Eleventh OOPSLA workshop on behavioral semantics: serving
31 542 the customer. Seattle, Washington, Boston: Northeastern University 2002:16–32.
32 543
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34 544
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3 561 **Figure 1:** Time schedule and study episodes for CADDIE2 trial
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5 562 **Figure 2:** Digital documentation form (based on openEHR data repository)
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For peer review only

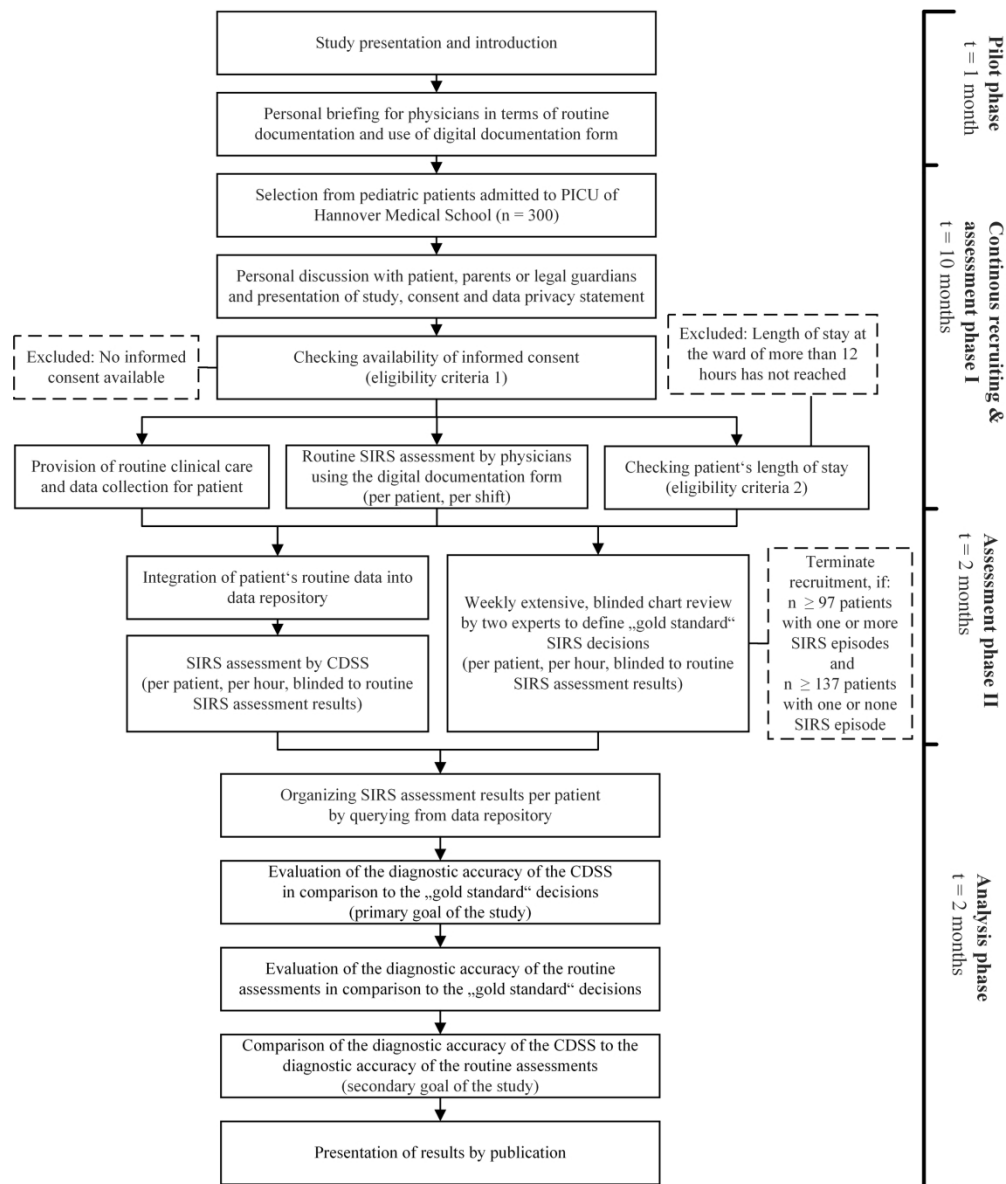


Figure 1: Time schedule and study episodes for CADDIE2 trial

208x245mm (300 x 300 DPI)

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* Patient (Firstname Lastname):

* SIRS/No SIRS?: SIRS No SIRS

* Shift: Weekend day shift Weekend night shift Early shift
 Late shift Night shift

* on day:

* Patient (Firstname Lastname):

* SIRS/No SIRS?: SIRS No SIRS

* Shift: Weekend day shift Weekend night shift Early shift
 Late shift Night shift

* on day:

∨ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

* SIRS/Organdysfunction?: SIRS Organdysfunction

Origin: infectious noninfectious

Comment:

∨ SIRS AND ORGANDYSFUNCTIONS (ADD MORE WITH +/-)

* SIRS/Organdysfunction?: SIRS Organdysfunction

Type: respiratory cardiovascular renal hematologic
 hepatic

Comment:

Figure 2: Digital documentation form (based on openEHR data repository)

90x109mm (300 x 300 DPI)

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1___
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3___
	2b	All items from the World Health Organization Trial Registration Data Set	___NA___
Protocol version	3	Date and version identifier	___3___
Funding	4	Sources and types of financial, material, and other support	___18___
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	___1,18___
	5b	Name and contact information for the trial sponsor	___NA___
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	___18___
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	___9,15,16_

1 **Introduction**

2

3 Background and rationale 6a Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention _____5,6,7__

4

5

6 6b Explanation for choice of comparators _____5,6,7,8__

7

8 Objectives 7 Specific objectives or hypotheses _____7,8_____

9

10 Trial design 8 Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) _____8_____

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14 **Methods: Participants, interventions, and outcomes**

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16 Study setting 9 Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained _____8_____

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19 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) _____9_____

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22 Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered NA (no interventions, diagnostic study), alternative: _____8_____

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29 11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) _____NA (each patient will be assessed by both diagnostic approaches), alternative: _____8_____

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	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_____NA (no intervention, routine care), alternative: _____16_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_____10_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_____9,10_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_____10,11,12_____
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_____9,10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_____12,13_____

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____NA_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____NA_____

1	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____7,11,16_
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4		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____16_____
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8 **Methods: Data collection, management, and analysis**

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10	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____13,14_
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15		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_____NA (no interventions)_
16				
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19	Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_____13,14, 15_
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23	Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_____9,10_
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26		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_____NA_____
27				
28		20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_____NA_____
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32 **Methods: Monitoring**

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34	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	_____15_____
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40		21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_____NA_____
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1	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	____15____
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4	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	____15,16_
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8	Ethics and dissemination			
9				
10	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	____16, 18, 19, Additional file 3____
11				
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14	Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	____19____
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18	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	____12,13____
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22		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	____NA____
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25	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	____13,15____
26				
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28	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	____18____
29				
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31	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	____18____
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34	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	____NA____
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38	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	____11,16____
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1	31b	Authorship eligibility guidelines and any intended use of professional writers	_____18_____
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3	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	_____NA_____
4			
5	Appendices		
6			
7	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
8			_____Additional
9			file 2_____
10	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable
11			_____NA_____
12			

14 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 15 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 16 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](#)" license.
 17

Patient Information (Parents)

Dear parents,

we would like to include your child in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

Your child was or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. Due to necessary monitoring and therapy we will gather laboratory results and vital signs continually.

During the clinical trial these laboratory and monitoring details will be analyzed with regard to a pronounced, generalized inflammatory reaction (Systemic inflammatory response syndrome (SIRS)) using the support of a computer-based system. The objective is to support the doctors in early recognition of SIRS.

The recognition of SIRS on a PICU is a complex task that is quite suitable for a Clinical Decision-Support System. SIRS is caused by different reasons, for example surgery, injuries or infection. It is a typical occurrence at PICU-patients and puts the patient under additional strain independent from the original reason for admittance. For diagnosing SIRS in paediatric patients correctly we have to find abnormalities in different vital signs and laboratory results which have age related reference values, making it an advanced task.

The development and clinical trial of a CDSS for SIRS in paediatric patients is the result of a cooperation between the Department of Paediatric Cardiology and Intensive Care Medicine of Medizinische Hochschule Hannover and the Peter L. Reichertz Institut für

1
2
3 Medizinische Informatik der Technischen Universität Braunschweig und der
4 Medizinischen Hochschule Hannover (PLRI).
5
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8 **Are there any risks by taking part in the clinical trial?**
9

10 The CDSS will only analyze data that is taken and saved during your child's admittance
11 on the PICU anyway. There won't be any additional blood tests, monitoring or
12 examinations. These standardized raised data will be saved in a pseudonymized way
13 that ensures the patient's privacy.
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18 **What happens if I don't agree to take part in the clinical trial?**
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20 The whole team will respect your decision if you do not want your child to take part in
21 the clinical trial. This will not be evaluated or have any negative effect on your child's
22 treatment. You can also revoke your agreement anytime.
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27 **Privacy Policy**
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29 The data raised and saved for the trial are pseudonymized and it is impossible to
30 reconnect them to an individual. The data will be saved for 10 years and deleted
31 afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.
32
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38 I received the information and consent to the clinical trial mentioned above.
39

40 Yes

No
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48 _____
49 (Date and signature of the parent/legal guardian)
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56 _____
57 (Date and signature of the medical doctor)
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Patient Information (Patient)

Dear patient,

we would like to include you in a clinical trial, you will find the details on the following pages. Please read them carefully. If you have any questions please do not hesitate to ask the doctor in charge.

Information about the clinical trial which is named:

Evaluation of the diagnostic accuracy of a Clinical Decision-Support System (CDSS) to support recognition of SIRS and Sepsis in paediatric intensive care patients in comparison to medical specialists.

You were or will be admitted on the paediatric intensive care unit (PICU) at Medizinische Hochschule Hannover. To treat you best we will monitor your vital signs as heartbeat, blood pressure and respiratory rate and take blood tests to monitor your white blood count and other inflammatory parameters. The results will be saved.

We know about the occurrence of extreme inflammatory reactions in paediatric patients. These can be caused by several reasons as surgery, injury or infection. We can measure these by changes in your vital signs, temperature or white blood count.

With a clinical trial something new is tested, for example some treatment. For this clinical trial your monitoring or vital sign data will be analyzed by a computer programme to support your doctors to detect changes that might be caused by an inflammatory reaction as soon as possible. The sooner we are aware we can adjust your treatment.

Are there any risks by taking part in the clinical trial?

The CDSS will only analyze data that is taken and saved during your admittance on the PICU anyway. There won't be any additional blood tests, monitoring or examinations. These standardized raised data will be saved in a pseudonymized way that ensures the patient's privacy.

What happens if I don't agree to take part in the clinical trial?

The whole team will respect your decision if you do not want to take part in the clinical trial. This will not be evaluated or have any negative effect on your treatment. You can also revoke your agreement anytime.

Privacy Policy

The data raised and saved for the trial are pseudonymized and it is impossible to reconnect them to an individual. The data will be saved for 10 years and deleted afterwards. The issues of the Bundesdatenschutzgesetz are considered in every respect.

I received the information and consent to the clinical trial mentioned above.

Yes

No

(Date and signature of the patient)

(Date and signature of the medical doctor)