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Epidemiology of injuries, treatment (costs), and outcome in burn patients admitted to a hospital with or without dedicated Burn Center (Burn-Pro); Protocol for a multicenter prospective observational study

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1 **Epidemiology of injuries, treatment (costs), and outcome in burn patients**
2 **admitted to a hospital with or without dedicated Burn Center (Burn-Pro);**
3 **Protocol for a multicenter prospective observational study**
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73 **Abstract**

74 **Introduction**

75 Admission to a Burn Center is indicated for patients with severe burns or with specific
76 characteristics like older age or comorbidities. The Emergency Management of Severe Burns
77 (EMSB) referral criteria have been implemented for optimal triaging of burn patients.
78 Extensive injury and outcome registration exists for patients admitted to a dedicated Burn
79 Center, but limited information is available about the organization of care and referral of burn
80 patients presented to a hospital elsewhere. The aims of this study are to compare the burn
81 injury characteristics, treatment (costs), Quality of Life, and scar quality of burn patients
82 admitted to a hospital without dedicated Burn Center versus burn patients with <10% Total
83 Body Surface Area (TBSA) burned who are admitted (or secondarily referred) to a Burn
84 Center. If these admissions were in agreement with the EMSB referral criteria will also be
85 determined.

86 **Methods and analysis**

87 In this multicenter, prospective, observational study (cohort study), the following two groups
88 of patients will be followed; 1) All patients (no age limit) admitted with burn-related injuries
89 to a hospital without a dedicated Burn Center in the Southwest Netherlands or Brabant
90 Trauma Region ; and 2) All patients (no age limit) with <10% Total Body Surface Area
91 (TBSA) burned who are primarily admitted (or secondarily referred) to the Burn Center of
92 Maasstad Hospital. Data on the burn injury characteristics (primary outcome), EMSB
93 compliance, treatment, treatment costs, and outcome will be collected from the patients'
94 medical files. At three weeks and at three, six, and 12 months after trauma, patients will be
95 asked to complete the Quality of Life (EuroQoL-5D; EQ-5D), and the patient-reported part of
96 the Patient and Observer Scar Assessment Scale (POSAS). At those time visits, the

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3 97 coordinating investigator or research assistant will complete the observer-reported part of the
4
5 98 POSAS.

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7 99 **Ethics and dissemination**

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9 100 This study has been exempted by the medical research ethics committee (MREC) Erasmus
10
11 101 MC (Rotterdam, The Netherlands). Each participant will provide written consent to
12
13 102 participate and remain encoded during the study. The results of the study are planned to be
14
15 103 published in an international, peer-reviewed journal.

16
17 104 **Registration details**

18
19 105 The study is registered at the Netherlands Trial Register (NTR6565; date 12-jul-2017).
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23
24 107 **Keywords**

25
26 108 Burn; Costs; Epidemiology; Etiology; Outcome; Quality of Life; Referral; Scar; Treatment.
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3 110 **Article Summary**
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6 111 **Strengths and limitations of this study:**
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- 8 112 - This study will provide insight into care of burn patients both in hospitals with and
9
10 113 without a dedicated Burn Center
11
12 114 - It is a prospective, multicenter, observational study with a strong methodological design.
13
14 115 - Participation of over 20 participating hospitals will increase the reliability and
15
16 116 generalizability of the data
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18 117 - Although the study will be mostly relevant for the Netherlands, it is also informative for
19
20 118 other regions.
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120 **Introduction**

121 Burns cause significant morbidity and mortality worldwide. Globally, some studies are
122 available on the epidemiology of Emergency Department (ED) treatments of burn injuries[1-
123 6]. These studies focus on epidemiology, including incidence rates and trends of burn-related
124 ED visits[3, 4, 6]. Two international publications have been written, including presentation of
125 data on ED treatment for burns in the Netherlands[7, 8]. These data were limited to home and
126 leisure accidents; work-related burn injuries were not included.

127
128 Depending on the severity, burn injuries may require specialized burn care. Three Dutch Burn
129 Centers have been established in order to provide specialized burn care to specific patients. In
130 order to enable proper triaging and referral, the Emergency Management of Severe Burns
131 (EMSB) referral criteria have been implemented (Table 1)[9]. This should result in optimal
132 treatment for burn patients.

133
134 In 2014, 322 patients with burns or inhalation injury were admitted to a hospital in the trauma
135 region South-West Netherlands. Of these patients, 213 (66%) were admitted to Burn Center
136 of Maastad Hospital (Rotterdam), the other 109 (34%) were admitted to hospitals without
137 specialized Burn Center. Whether or not these 109 admissions were in compliance with the
138 EMSB referral criteria is unknown. Equally important, there is a lack of insight into the
139 epidemiology, treatment (including treatment costs), and outcome (both clinical results and
140 Quality and Life) of the patients treated in hospitals without Burn Center. One study is
141 currently being conducted, in which treatment, Quality of Life, and medical costs of patients
142 reporting with burn injuries to the Emergency Department is studied[10]. The study
143 population (N=87) mainly consists of non-admitted patients.

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3 145 In order to get insight into the epidemiology of burn patients, detailed data collection on
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5 146 patient characteristics, etiology, burn injury characteristics, treatment, and outcome is critical.
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7 147 For that reason, the Dutch Burn Repository (DBR) R3 has been established in 2009[11]. From
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9 148 that date onwards, all patients admitted to a Burn Center in The Netherlands are registered in
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11 149 this Repository. Burn patients admitted elsewhere are not included in the R3 Repository.

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16 151 Three other national registries also do not provide insight into epidemiology, treatment (costs)
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18 152 and outcome including quality of life of all admitted burn patients. The National Injury
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20 153 Surveillance System (in Dutch: Letsel Informatie Systeem, LIS; www.veiligheid.nl)[12] and
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22 154 the National Medical Registration (in Dutch: Landelijke Medische Registratie, LMR;
23
24 155 www.dutchhospitaldata.nl)[13] register non-admitted and admitted patients, respectively.

25
26 156 Both are insufficient, as they register patients based on the main diagnosis, which may not
27
28 157 always be the burn injury. The Dutch National Trauma Registry (in Dutch: Landelijke
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30 158 Trauma Registratie, LTR; www.lnaz.nl) registers all admitted trauma patients. It encodes burn
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32 159 wounds, but with limited detail, and does not contain relevant treatment and outcome data.

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37 161 Based on the above, there are currently no data available that provide sufficient details about
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39 162 patients admitted to a hospital without Burn Center. The main aim of this study is to compare
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41 163 the burn injury characteristics of burn patients admitted to a hospital without dedicated Burn
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43 164 Center versus burn patients with <10% Total Body Surface Area (TBSA) burned who are
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45 165 admitted (or secondarily referred) to a Burn Center. Secondary aims are 1) to determine if
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47 166 these admissions were in agreement with the EMSB referral criteria; and 2) to compare the
48
49 167 treatment and direct medical costs between these patient groups, and to compare the Quality
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51 168 of Life (EuroQoL-5D; EQ-5D), and scar quality (Patient and Observer Scar Assessment
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53 169 Scale; POSAS) between these patient groups until 12 months follow-up.

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171 **Methods and analyses**

172 **Study design**

173 This study will follow a multicenter, prospective, observational study design (*i.e.*, cohort
174 study). Patients will be recruited from every hospital in two large trauma regions in The
175 Netherlands, the South-West Netherlands trauma region and Network Emergency Care
176 Brabant. The Burn Center of Maasstad Hospital is included in the South-West Netherlands
177 trauma area. The following 18 hospitals in The Netherlands will participate: Admiraal De
178 Ruyter Ziekenhuis (Goes), Albert Schweitzer Ziekenhuis (Dordrecht), Amphia Ziekenhuis
179 (Breda), Beatrix Ziekenhuis (Gorinchem), Bravis Ziekenhuis (Roosendaal), Catharina
180 Ziekenhuis (Eindhoven), Elisabeth-TweeSteden Ziekenhuis (Tilburg), Elkerliek Ziekenhuis
181 (Helmond), Erasmus MC, University Medical Center (Rotterdam), Franciscus Gasthuis &
182 Vlietland (Rotterdam), IJsselland Ziekenhuis (Capelle aan de IJssel), Ikazia Ziekenhuis
183 (Rotterdam), Jeroen Bosch Ziekenhuis ('s-Hertogenbosch), Burn Center Maasstad Hospital
184 (Rotterdam), Máxima Medisch Centrum (Veldhoven), Van Weel-Bethesda Ziekenhuis
185 (Dirksland), and ZorgSaam Zeeuws-Vlaanderen (Terneuzen).

186 The study is registered at the Netherlands Trial Register (NTR6565; date 12-jul-2017).

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188 **Recruitment and informed consent**

189 Eligible persons admitted with burn-related injuries (or the parents of pediatric patients) will
190 be informed about the study as soon as possible after hospital presentation. They may receive
191 the information at the ED or while admitted at the surgical ward. The local staff will ask
192 permission to send contact details to the research team. Upon receipt of that permission, a
193 local contact person in the participating hospital will provide details of the patient to the
194 research team. The coordinating investigator or research assistant will contact the patient (or
195 parents) to explain the study, and will send the information brochure and informed consent

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3 196 form. The coordinating investigator or a research assistant will attend the patient's outpatient
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5 197 visit in the hospital (at approximately three weeks after admission) in order to further explain
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7 198 the study, answer any question the patient (or parents) may have, and for signing informed
8
9 199 consent. This gives patients on average two to three weeks to consider their participation. As
10
11 200 data collection also includes investigation of the TBSA and extent of burn wounds, it is not
12
13 201 possible to give patients more time to consider their participation.

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15 202 In order to reduce bias as much as possible, the follow-up measurements by the
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17 203 clinical investigator or research assistant will be performed using a standardized protocol.
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22 205 **Study population**

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24 206 The study population will consist of a group of patients admitted to a hospital without
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26 207 dedicated burn center or who are admitted to a dedicated burn center. In order to be eligible to
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28 208 participate in this study, a subject must meet all of the following criteria:

29
30 209 1) Patients with burn-related injuries (no age limit), admitted to a hospital without dedicated

31
32 210 Burn Center in the trauma regions South-West Netherlands or Brabant; or patients with

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34 211 <10% TBSA burned, who are primarily admitted or secondarily referred to the Burn

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36 212 Center of Maastad Hospital*

37
38 213 2) Provision of informed consent

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40 214 * 10% has been chosen as we expect that patients admitted outside the Burn Centers will have

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42 215 no more than 10% TBSA burned.
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48 217 A potential subject who meets any of the following criteria will be excluded from

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50 218 participation in this study:

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52 219 1) Patients who died <24 hours due to severity of non-burn injuries

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54 220 2) Patients with incomplete or unknown contact information
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3 221 3) Insufficient comprehension of the Dutch or English language to understand the
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5 222 questionnaires

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9 224 **Outcome measures**

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11 225 The burn-related injury pattern will serve as primary outcome measure. Information on the
12
13 226 following items will be collected from the patients' medical files:

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15 227 - Burn etiology (scald, flame, contact, chemical, or other)
16
17 228 - Inhalation injury (yes or no)
18
19 229 - Setting (home, work, or other)
20
21
22 230 - Body regions burned, severity (% TBSA burned)
23
24 231 - Extent of burns (superficial dermal, deep dermal, or subdermal)

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27
28 233 The secondary outcome measures are:

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30 234 1) Compliance with EMSB referral criteria (yes or no)
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32 235 2) Treatment
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34 236 3) Health care use in hospital with associated treatment costs
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36 237 4) Health-Related Quality of life (EuroQol-5D-3L (EQ-5D-3L))
37
38 238 5) Patient and Observer Scar Assessment Scale (POSAS)

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43 240 The following treatment characteristics will be collected:

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45 241 - Prehospital transport (ambulance, helicopter emergency medical services, or other
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47 242 - Level of trauma care (level 1, 2, or 3)
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49 243 - Required care (ward or Intensive Care Unit)
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51 244 - Resuscitation (amount of fluid <24h after admission)
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53 245 - Intubation (yes or no)
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- 246 - Bronchoscopy (yes or no)
- 247 - Wound treatment (wound dressing, topical therapy, or other)
- 248 - Date of the first operation
- 249 - Escharotomy (yes or no)
- 250 - Type of operation (split skin grafting, full thickness skin grafting, or excision and
- 251 primary closure)
- 252 - % TBSA that needed skin grafting
- 253 - Expansion of split skin graft (1:1, 1:1.5, 1:3, or 1:6)
- 254 - Total number of operations
- 255 - Indication for second, third, and any subsequent operation
- 256 - Number of outpatient department visits
- 257 - Date of discharge from hospital
- 258 - Reconstructive surgery (release/excision with split skin grafting, full thickness grafting,
- 259 or laps)

260

261 In order to determine the treatment costs, the use of hospital resources will be collected from
262 medical files directly. All direct medical costs due to treatment, complications, and events
263 during follow-up (*e.g.*, ED visit, diagnostic work-up, therapy, events, surgery, admissions,
264 follow-up visits) will be collected. The economic evaluation will be in accordance with the
265 Dutch guideline and will use cost prices where possible[14]. Medical costs will be calculated
266 by multiplying the volumes of health care use with the corresponding unit prices.

267

268 The EQ-5D is a validated questionnaire for measuring health-related quality of life[15, 16].
269 Its use is recommended for the assessment of quality of life in trauma patients, especially for
270 economic assessments[17, 18]. The EQ-5D-3L descriptive system consists of five dimensions

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3 271 of health (mobility, self-care, usual activities, pain/discomfort anxiety/depression), each with
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5 272 three possible answers. Scores are converted to a utility score ranging from zero to one, with
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7 273 lower scores indicating poorer quality of life. The EQ Visual Analog Score (VAS) records the
8
9 274 respondents self-rated health status on a vertical (0-100) visual analog scale. Patients aged 16
10
11 275 years or older will be asked to complete the EQ-5D themselves. Pediatric patients (<16 years)
12
13 276 will be asked to complete the youth version of the EQ-5D, or their parent(s) will be asked to
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15 277 complete a proxy version of the EQ-5D youth version.
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20 279 The POSAS v2.0 (www.posas.org)[19] consists of two parts: a Patient Scale and an Observer
21
22 280 Scale, which aim to provide a rating of several measured of scar quality (vascularity,
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24 281 pigmentation, relief/texture, thickness, pliability, surface area, pain, and itching/pruritus).
25
26 282 Patients aged 16 years or older and parents of younger pediatric patients will complete the
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28 283 patient-reported part, a trained observer will complete the observer-reported part.
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32 33 285 **Other data collected**

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35 286 The following, additional, data will be collected in order to describe the study population,
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37 287 patient characteristics, additional injury characteristics, and burn-related (adverse) events:
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39 288 - Patient characteristics: age, gender, American Society of Anesthesiologists (ASA)
40
41 289 classification, comorbidities (diabetes or other)
42
43 290 - Additional injury characteristics: Injury Severity Score (ISS), Abbreviated Injury Score
44
45 291 (AIS), for all nine anatomical regions as registered in the trauma registry)
46
47 292 - Burn-related (adverse) events: hematoma (yes or no), excessive blood loss (requiring
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49 293 blood transfusion), wound infection (requiring antibiotic and/or surgical treatment) (yes
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51 294 or no), pneumonia (yes or no), graft loss requiring surgical intervention (or vac therapy;
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53 295 yes or no), or other.
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3 296 - Outcome related variables: duration of hospital admission, time to wound closure
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5 297 (calculated from date of admission and date of last wound dressing), percentage graft take
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7 298 5-7 days post burn, discharge destination (home, other hospital, Burn Center,
8
9 299 rehabilitation facility, or other), and mortality (possibly burn-related yes or no)
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11 300

13 301 **Study procedures**

15 302 Patients will be followed for one year, with visits planned at three weeks (window 2-4
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17 303 weeks), three months (window 11-15 weeks), six months (window 5-7 months), and 12
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19 304 months (window 12-14 months) after admission (Table 2). One additional, optional visit is
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21 305 planned at six weeks (window 5-7 weeks) in case the burn wound has not closed at three
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23 306 weeks. The coordinating investigator or research assistant will be present at each outpatient
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25 307 department visit of the enrolled patients for direct collection of data. The study will not
26
27 308 interfere with treatment or follow-up.

30 309 Patient characteristics, injury characteristics, and any other relevant data will be
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32 310 collected from the patient's medical files as soon as possible after signing informed consent.
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34 311 Treatment and other clinical data such as adverse events will be collected (partly from the
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36 312 patient files) at each follow-up visit. During these regular clinical visits, any radiographs or
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38 313 digital photos that are routinely obtained will be collected. For the purpose of the study,
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40 314 additional details concerning treatment and outcome that are not mentioned in the patient's
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42 315 hospital files, may be registered on the case report forms directly. At the one-year follow-up
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44 316 visit, the coordinating investigator or research assistant will document any secondary
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46 317 intervention that may be planned for the patient.

49 318 As soon as possible after inclusion, patients will be asked to complete the EQ-5D-3L
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51 319 reflecting their pre-injury quality of life. At three months, six months, and at 12 months after
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53 320 the primary hospital admission, patients (or the parents of pediatric patients) will be asked to
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3 321 complete the EQ-5D-3L and the patient-reported part of the POSAS. The coordinating
4
5 322 investigator or research assistant will complete the physician-reported part of the POSAS.

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8 9 324 **Sample size calculation**

10
11 325 A formal sample size calculation for this observational study is not constructive. By including
12
13 326 all patients treated in the trauma regions South-West Netherlands and Brabant during 18
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15 327 months, as well as all patients with >10% TBSA burned who are primarily admitted or
16
17 328 secondarily referred to a Burn Center, the maximum number of inclusions will be achieved.
18
19 329 The larger the number of patients, the more reliable the analysis will be. Enrolling all patients
20
21 330 possible will result in the highest reliability of data (*i.e.*, accurate point estimate with lowest
22
23 331 possible variance). Based on the data in the annual report of Trauma Center South-West
24
25 332 Netherland (*i.e.*, 109 patients admitted outside the Burn Center in the year 2014), we expect to
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27 333 include approximately 300 patients in 18 months in the two trauma regions combined.
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30 31 32 33 335 **Statistical analysis**

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35 336 Data will be analyzed using the Statistical Package for the Social Sciences (SPSS) version
36
37 337 21.0 or higher (SPSS, Chicago, Ill., USA) and will be reported following the Strengthening
38
39 338 the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Missing
40
41 339 values will not be replaced by imputation. Normality of continuous data will be tested with
42
43 340 the Shapiro-Wilk test, and homogeneity of variances will be tested using the Levene's test. A
44
45 341 p-value <0.05 will be taken as threshold of statistical significance in all statistical tests, and all
46
47 342 tests will be two-sided. No interim analysis is planned.

48
49 343 First, descriptive analysis will be performed in order to report the outcome measures
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51 344 and other collected data. For continuous data (*e.g.*, EQ-5 and POSAS, the mean and SD
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53 345 (parametric data) or the median and quartiles (non-parametric data) will be reported. The only
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55 346 exception are cost data, these will be reported as mean with 95% confidence interval (95%

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3 347 CI). The 95% CI around the mean costs will be approximated by nonparametric
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5 348 bootstrapping. For categorical data (*e.g.*, EMSB compliance), the number and frequencies will
6
7 349 be reported. Data will be reported for the entire population as well as separately for the group
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9 350 of patients admitted to a hospital without versus with a Burn Center.

11 351 Next univariate analysis will be done. Statistical significance of difference between the
12
13 352 two groups will be tested using a Student's T-test (parametric, continuous data; with or
14
15 353 without equal variance assumed as applicable), Mann-Whitney U-test (non-parametric,
16
17 354 continuous data), or Chi-squared or Fisher's Exact test (categorical data, as applicable).

20 355 Subgroups will be determined based on the patients included. Relevant subgroups can
21
22 356 be children versus adults versus elderly, subgroups with different percentages TBSA burned,
23
24 357 or patients admitted in compliance versus disagreement with the EMSB referral criteria.
25
26 358 Should formal testing between the latter two subgroups be feasible, this will be done as
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28 359 described above.

31 360 The economic evaluation will include costs for health care. Direct and indirect,
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33 361 medical and non-medical cost will be measured as indicated in the Dutch guidelines for
34
35 362 economic evaluations, using standard, published cost prices where possible[14].

37 363

364 **Ethics and dissemination**

365 This study will be conducted according to the principles of the Declaration of Helsinki (64th
366 World Medical Association General Assembly, Fortaleza, Brazil, October 2013). Data will
367 encoded and stored in a pass-word protected OpenClinica database with restricted access to
368 the researchers only. Data will be entered ones. Quality of the entered data will be monitored
369 by checking entry for a random sample of patients prior to database locking.

370 This study has been exempted by the medical research ethics committee (MREC)
371 Erasmus MC (Rotterdam, The Netherlands). This MREC acts as central ethics committee for
372 this trial (reference number MEC-2017-356). Approval has been obtained from the local
373 hospital boards in all participating centers. Following review of the protocol (version 1.0 date
374 22-may-2017, the MREC concluded that this study is not subject to the Medical Research
375 Involving Human Subjects Act (WMO). They concluded that the study is a medical/scientific
376 research, but no patients are subjected to procedures or are required to follow rules of
377 behavior. Consequently, the statutory obligation to provide insurance for subjects
378 participating in medical research (article 7 of the WMO) does not apply. Any important
379 changes in the protocol will be submitted to the accredited MREC. The results of the study
380 are planned to be published in an international, peer reviewed journal and presented at
381 national and international trauma and burn care meetings. Each participating center will
382 provide a group author to every publication. No personal data of study participants will be
383 presented.

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3 385 **Discussion**
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5 386 Burns cause significant morbidity and mortality worldwide, and depending on the severity,
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7 387 burn injuries may require specialized burn care in a dedicated Burn Centers. In order to enable
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9 388 optimal triaging and referral to a Burn Center, the EMSB referral criteria have been
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11 389 implemented[9]. Whereas extensive injury and outcome registration exists for patients
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13 390 admitted to a dedicated Burn Center, there are currently no data available that provide
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15 391 sufficient details about patients admitted to a hospital without Burn Center. Successful
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17 392 completion of this study will provide more insight into the percentage of patients admitted to
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19 393 a hospital without dedicated Burn Center. It will also provide us detailed data on patient and
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21 394 injury characteristics, EMSB compliance, treatment, treatment costs, relevant outcome data,
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23 395 and quality of life of burn patients with primary admission at a hospital without Burn Center
24
25 396 as well as patients with <10% TBSA burned who are secondarily referred to a Burn Center.
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27 397 Twenty-one hospitals will participate. Inclusion has started September 18, 2017, and a total of
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29 398 39 patients have been included so far. Eighteen months are planned for inclusion. With a
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31 399 follow-up of one year the presentation of data will be expected by the end of 2020.
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449 **List of abbreviations used**

450 AIS, Abbreviated Injury Scale; ASA classification, American Society of Anesthesiologists
451 classification; 95%CI, 95% Confidence Interval; DBR R3, Dutch Burn Repository R3; ED,
452 Emergency Department; EMSB, The Emergency Management of Severe Burns; EQ-5D,
453 EuroQoL-5D; ISS, Injury Severity Score; LIS, Letsel Informatie Systeem (in English:
454 National Injury Surveillance System); LMR, Landelijke Medische Registratie (in English:
455 National Medical Registration); LNAZ, Landelijke Netwerk Acute Zorg (in English: National
456 Network Acute Care); LTR, Landelijke Trauma Registratie (in English: National Trauma
457 Registry); MEC, Medisch Ethische Commissie (in English: Medical Research Ethics
458 Committee (MREC); NTR, Nederlands Trial Register (in English; Netherlands National Trial
459 Register); POSAS, Patient and Observer Scar Assessment Scale; QoL, Quality of Life; SD,
460 Standard Deviation; SPSS, Statistical Package for the Social Sciences; STROBE,
461 STrengthening the Reporting of OBservational studies in Epidemiology; TBSA, Total Body
462 Surface Area; VAS, Visual Analog Scale; WMO, Medical Research Involving Human
463 Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen).

465 **Competing interests**

466 The authors declare that they have no competing interests.

468 **Authors' contributions**

469 CHVDV, DTVY, MVB, SP, EMMV and MJHV developed the study. DTVY and EMMVL
470 drafted the manuscript. MHJV will act as trial principal investigator. DTVY, DB, AYMVPC,
471 PARDR, MG, TMALK, KWVL, ANR, MS, LVDS, AHVDV, FCVE, PVVE, PAV, DIV,
472 MW, CHVD and MHJV will participate in patient inclusion and outcome assessment. DTVY

1
2
3 473 and EMMVL will perform statistical analysis of the study data. All authors have read and
4
5 474 approved the final manuscript.

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7 475

8 9 476 **Funding statement**

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11
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13
14 478 (ADBC; Beverwijk, The Netherlands; reference number WO/16.110).

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17 18 19 480 **Competing interests statement**

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21 481 The authors declare that they have no competing interests.
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482 **Tables**483 **Table 1: EMSB referral criteria**[9]

1)	The percentage Total Body Surface Area burned (TBSA burned; >10% TBSA in adults or >5% in children)
2)	Burns of special areas (face, hands, feet, perineum, genitalia, and major joints)
3)	Full thickness burns >5% TBSA burned
4)	Electrical burns
5)	Chemical burns
6)	Burns with associated inhalation injury
7)	Circumferential burns of limbs or chest
8)	Extremes of age (children and elderly)
9)	Pre-existing medical disorders which could complicate management and prolong recovery or effect mortality
10)	Associated trauma

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485 **Table 2: Schedule of events**

Event forms	Screening	3 we (2-4 we)	6 we* (5-7 we)	3 mo (11-15 we)	6 mo (6-7 mo)	12 mo (12-14 mo)
Screening	X					
Informed Consent		X				
Patient characteristics		X				
Injury characteristics		X				
Radiology		X ¹	X ¹	X ¹	X ¹	X ¹
Digital photo		X ¹	X ¹	X ¹	X ¹	X ¹
Treatment characteristics		X	X	X	X	X
Outcome details		X	X	X	X	X
Adverse Events		X	X	X	X	X
Clinical FU		X	X	X	X	X
Health Care Consumption		X	X	X	X	X
EQ-5D		X ²		X	X	X
POSAS				X	X	X
Early withdrawal		**	**	**	**	**

486 *Optional visit; will only take place if wounds are not closed at three weeks.

487 ¹Only if treating surgeon requests these images.488 ²Asking for EQ-5D pre-burn.

489 ** Only at time of withdrawal.



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	5, 9
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	17
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 2, 3
	5b	Name and contact information for the trial sponsor	1
	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	21, 22
	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)	21, 22

Introduction

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	4, 7, 8
	6b	Explanation for choice of comparators	N.A.
Objectives	7	Specific objectives or hypotheses	4, 8
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)	9

Methods: Participants, interventions, and outcomes

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	10
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)	10, 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	11-15
	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)	N.A.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	N.A.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
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	11-14
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)	14, 15, Table 2

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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	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	

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	N.A.
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	N.A.
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N.A.
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N.A.
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.

Methods: Data collection, management, and analysis

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	11-15
	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	

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3	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	17
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7	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	15-16
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10		20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
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12		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)	15
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15	Methods: Monitoring			
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17	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	N.A.; instead, quality checks of entered data are planned (page 17)
18				
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22		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	15
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25	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	N.A. is not an intervention study
26				
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28	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
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32	Ethics and dissemination			
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34	Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5, 17
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37	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)	17
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3	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9-10
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N.A.
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9	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	17
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12	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
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15	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	17
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18	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	N.A.
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21	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	17
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25		31b	Authorship eligibility guidelines and any intended use of professional writers	17
26				
27		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N.A.
28				
29	Appendices			
30				
31	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Attached
32				
33				
34	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	N.A. _____
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37 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items.
 38 Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons
 39 "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.
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BMJ Open

Epidemiology of injuries, treatment (costs), and outcome in burn patients admitted to a hospital with or without dedicated Burn Center (Burn-Pro); Protocol for a multicenter prospective observational study

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2018-023709.R1
Article Type:	Protocol
Date Submitted by the Author:	21-Aug-2018
Complete List of Authors:	<p>Van Lieshout, Esther M.M.; Erasmus MC, University Medical Center Rotterdam</p> <p>Van Yperen, Daan; Maasstad Ziekenhuis, Burn Center; Erasmus MC, Trauma Research Unit Department of Surgery</p> <p>Van Baar, Margriet; Maasstad Ziekenhuis, Burn Center; Erasmus MC, Department of Public Health</p> <p>Polinder, Suzanne; Erasmus MC, Department of Public Health</p> <p>Boersma, Doeke; Jeroen Bosch Ziekenhuis, Department of Surgery</p> <p>Cardon, Anne; ZorgSaam, Department of Surgery</p> <p>De Rijcke, Piet; IJsselland Ziekenhuis, Department of Surgery</p> <p>Guijt, Marc; Elkerliek Ziekenhuis, Department of Surgery</p> <p>Klem, Taco; Sint Franciscus Gasthuis, Department of Surgery</p> <p>Lansink, Koen; Elisabeth-TweeSteden Ziekenhuis, Department of Surgery</p> <p>Ringburg, Akkie; Ikazia Ziekenhuis, Department of Surgery</p> <p>Staarink, Maarten; Van Weel-Bethesda Ziekenhuis, Department of Surgery</p> <p>Schoot, Leon; Rivas Zorggroep, Department of Surgery</p> <p>van der VEEN, Alexander; Catharina Ziekenhuis, Department of Surgery</p> <p>Van Eijck, Floortje; Bravis ziekenhuis, Department of Surgery</p> <p>Van Eerten, Percy; Maxima Medisch Centrum locatie Veldhoven, Department of Surgery</p> <p>Vegt, Paul; Albert Schweitzer Ziekenhuis, Department of Surgery</p> <p>Vos, DI; Amphia Ziekenhuis, Department of Surgery</p> <p>Waleboerg, Marco; Admiraal De Ruyter Ziekenhuis</p> <p>Verhofstad, Michael; Erasmus MC, University Medical Center Rotterdam, Trauma Surgery</p> <p>Van der Vlies, Cornelis; Maasstad Ziekenhuis, Burn Center; Erasmus MC, Trauma Research Unit Department of Surgery</p>
Primary Subject Heading:	Surgery
Secondary Subject Heading:	Epidemiology, Health economics
Keywords:	Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, WOUND MANAGEMENT, EPIDEMIOLOGY, HEALTH ECONOMICS, Trauma management < ORTHOPAEDIC & TRAUMA

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	SURGERY, SURGERY

SCHOLARONE™
Manuscripts

1 **Epidemiology of injuries, treatment (costs), and outcome in burn patients**
2 **admitted to a hospital with or without dedicated Burn Center (Burn-Pro);**
3 **Protocol for a multicenter prospective observational study**
4

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75 **Abstract**

76 **Introduction**

77 The Emergency Management of Severe Burns (EMSB) referral criteria have been
78 implemented for optimal triaging of burn patients. Admission to a Burn Center is indicated
79 for patients with severe burns or with specific characteristics like older age or comorbidities.
80 Patients not meeting these criteria can also be treated in a hospital without Burn Center.

81 Limited information is available about the organization of care and referral of these patients.

82 The aims of this study are to determine the burn injury characteristics, treatment (costs),
83 Quality of Life, and scar quality of burn patients admitted to a hospital without dedicated
84 Burn Center. These data will subsequently be compared with data from patients with <10%
85 Total Body Surface Area (TBSA) burned who are admitted (or secondarily referred) to a Burn
86 Center. If admissions were in agreement with the EMSB referral criteria will also be
87 determined.

88 **Methods and analysis**

89 In this multicenter, prospective, observational study (cohort study), the following two groups
90 of patients will be followed; 1) All patients (no age limit) admitted with burn-related injuries
91 to a hospital without a dedicated Burn Center in the Southwest Netherlands or Brabant
92 Trauma Region ; and 2) All patients (no age limit) with <10% Total Body Surface Area
93 (TBSA) burned who are primarily admitted (or secondarily referred) to the Burn Center of
94 Maastad Hospital. Data on the burn injury characteristics (primary outcome), EMSB
95 compliance, treatment, treatment costs, and outcome will be collected from the patients'
96 medical files. At three weeks and at three, six, and 12 months after trauma, patients will be
97 asked to complete the Quality of Life (EuroQoL-5D; EQ-5D), and the patient-reported part of
98 the Patient and Observer Scar Assessment Scale (POSAS). At those time visits, the

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2
3 99 coordinating investigator or research assistant will complete the observer-reported part of the
4
5 100 POSAS.

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7 101 **Ethics and dissemination**

8
9 102 This study has been exempted by the medical research ethics committee (MREC) Erasmus
10
11 103 MC (Rotterdam, The Netherlands). Each participant will provide written consent to
12
13 104 participate and remain encoded during the study. The results of the study are planned to be
14
15 105 published in an international, peer-reviewed journal.

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17
18 106 **Registration details**

19
20 107 The study is registered at the Netherlands Trial Register (NTR6565; date 12-jul-2017).

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24 109 **Keywords**

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26 110 Burn; Costs; Epidemiology; Etiology; Outcome; Quality of Life; Referral; Scar; Treatment.

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3 112 **Article Summary**
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6 113 **Strengths and limitations of this study:**
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- 8 114 - This study will provide insight into care of burn patients both in hospitals with and
9
10 115 without a dedicated Burn Center
11
12 116 - It is a prospective, multicenter, observational study with a best possible methodological
13
14 117 design.
15
16 118 - Participation of over 20 participating hospitals will increase the reliability and
17
18 119 generalizability of the data
19
20 120 - Although the study will be mostly relevant for the Netherlands, it is also informative for
21
22
23 121 other regions.
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123 **Introduction**

124 Burns cause significant morbidity and mortality worldwide. Globally, some studies are
125 available on the epidemiology of Emergency Department (ED) treatments of burn injuries[1-
126 8], including three from the Netherlands[7-9]. These data were limited to home and leisure
127 accidents; work-related burn injuries were not included.

128

129 Depending on the severity, burn injuries may require specialized burn care. In order to enable
130 proper triaging and referral, the Emergency Management of Severe Burns (EMSB) referral
131 criteria have been implemented (Table 1)[10].

132

133 In 2014, 322 patients with burns or inhalation injury were admitted to a hospital in the trauma
134 region South-West Netherlands. Of these patients, 109 (34%) were admitted to hospitals
135 without specialized Burn Center. There is a lack of insight into the epidemiology, treatment
136 (including treatment costs), and outcome (both clinical results and Quality and Life) of the
137 patients treated in hospitals without Burn Center.

138

139 In order to get insight into the epidemiology of burn patients, detailed data collection on
140 patient characteristics, etiology, burn injury characteristics, treatment, and outcome is critical.

141 Such data are currently not available from current registries. The Dutch Burn Repository

142 (DBR) R3 only registers data for patients admitted to a Burn Center[11]. The National Injury

143 Surveillance System (in Dutch: Letsel Informatie Systeem, LIS; www.veiligheid.nl)[12] and

144 the National Medical Registration (in Dutch: Landelijke Medische Registratie, LMR;

145 www.dutchhospitaldata.nl)[13] register non-admitted and admitted patients, respectively.

146 Both are insufficient, as they register patients based on the main diagnosis, which may not

147 always be the burn injury. The Dutch National Trauma Registry (in Dutch: Landelijke

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3 148 Trauma Registratie, LTR; www.lnaz.nl) registers all admitted trauma patients. It encodes burn
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5 149 wounds, but with limited detail, and does not contain relevant treatment and outcome data.

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9 151 Based on the above, there are currently no data available that provide sufficient details about
10
11 152 patients admitted to a hospital without Burn Center. It is also not clear if these are different
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13 153 for patients with similar burn injury severity admitted to a Burn Center. The main aim of this
14
15 154 study is to determine the burn injury characteristics of burn patients admitted to a hospital
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17 155 without dedicated Burn Center. Secondary aims are 1) to determine if these admissions were
18
19 156 in agreement with the EMSB referral criteria; 2) to determine the treatment and direct medical
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21 157 costs, the Quality of Life (EuroQoL-5D; EQ-5D), and scar quality (Patient and Observer Scar
22
23 158 Assessment Scale; POSAS) for these patients until 12 months follow-up; and 3) to compare
24
25 159 the injury pattern and outcome of these patients with burn patients with <10% Total Body
26
27 160 Surface Area (TBSA) burned who are admitted (or secondarily referred) to a Burn Center. We
28
29 161 expect that burn patient admission outside the Burn Center is restricted to a maximum of 10%
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31 162 TBSA, and that outcome is similar to that achieved for a subgroup with similar burn injury
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33 163 severity admitted to a Burn Center.
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165 **Methods and analyses**

166 **Study design and setting**

167 This study will follow a multicenter, prospective, observational study design (cohort study).
168 Patients will be recruited from every hospital in two large trauma regions in The Netherlands,
169 the South-West Netherlands trauma region and Network Emergency Care Brabant. The Burn
170 Center of Maasstad Hospital is included in the South-West Netherlands trauma area. The
171 following 18 hospitals in The Netherlands will participate: Admiraal De Ruyter Ziekenhuis
172 (Goes), Albert Schweitzer Ziekenhuis (Dordrecht), Amphia Ziekenhuis (Breda), Beatrix
173 Ziekenhuis (Gorinchem), Bravis Ziekenhuis (Roosendaal), Catharina Ziekenhuis
174 (Eindhoven), Elisabeth-TweeSteden Ziekenhuis (Tilburg), Elkerliek Ziekenhuis (Helmond),
175 Erasmus MC, University Medical Center (Rotterdam), Franciscus Gasthuis & Vlietland
176 (Rotterdam), IJsselland Ziekenhuis (Capelle aan de IJssel), Ikazia Ziekenhuis (Rotterdam),
177 Jeroen Bosch Ziekenhuis ('s-Hertogenbosch), Burn Center Maasstad Hospital (Rotterdam),
178 Máxima Medisch Centrum (Veldhoven), Van Weel-Bethesda Ziekenhuis (Dirksland), and
179 ZorgSaam Zeeuws-Vlaanderen (Terneuzen). The study started in September, 2017 and the
180 recruiting periods will be 18 months. With a follow-up of one year the presentation of data
181 will be expected by the end of 2020.

182

183 **Study registration**

184 The study is registered at the Netherlands Trial Register (NTR6565; date 12-jul-2017).

185

186 **Recruitment and informed consent**

187 Eligible persons admitted with burn-related injuries (or the parents of pediatric patients) will
188 be informed about the study as soon as possible after hospital presentation. They may receive
189 the information at the ED or while admitted at the surgical ward. The local staff will ask

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2
3 190 permission to send contact details to the research team. Upon receipt of that permission, a
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5 191 local contact person in the participating hospital will provide details of the patient to the
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7 192 research team. The coordinating investigator or research assistant will contact the patient (or
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9 193 parents) to explain the study, and will send the information brochure and informed consent
10
11 194 form. The coordinating investigator or a research assistant will attend the patient's outpatient
12
13 195 visit in the hospital (at approximately three weeks after admission) in order to further explain
14
15 196 the study, answer any question the patient (or parents) may have, and for signing informed
16
17 197 consent. This gives patients on average two to three weeks to consider their participation. As
18
19 198 data collection also includes investigation of the TBSA and extent of burn wounds, it is not
20
21 199 possible to give patients more time to consider their participation.
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24 200 In order to reduce bias as much as possible, the follow-up measurements by the
25
26 201 clinical investigator or research assistant will be performed using a standardized protocol.
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31 203 **Study population and eligibility criteria**

32 204 The study population will consist of a group of patients admitted to a hospital without
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34 205 dedicated burn center or who are admitted to a dedicated burn center. In order to be eligible to
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36 206 participate in this study, a subject must meet all of the following criteria:
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38

39 207 1) Patients with burn-related injuries (no age limit), admitted to a hospital without dedicated
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41 208 Burn Center in the trauma regions South-West Netherlands or Brabant; or patients with
42
43 209 <10% TBSA burned, who are primarily admitted or secondarily referred to the Burn
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45 210 Center of Maasstad Hospital*

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47 211 2) Provision of informed consent

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49 212 * 10% has been chosen as we expect that patients admitted outside the Burn Centers will have
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51 213 no more than 10% TBSA burned. This is also in line with the EMSB referral criteria[10]. The
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3 214 % TBSA will be assessed during physical examination by a research physician who has had
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5 215 elaborate training for this at the participating dedicated Burn Center.
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9 217 A potential subject who meets any of the following criteria will be excluded from
10
11 218 participation in this study:

12
13 219 1) Patients who died <24 hours due to severity of non-burn injuries (*e.g.*, severe head injury)

14
15 220 2) Patients with incomplete or unknown contact information

16
17 221 3) Insufficient comprehension of the Dutch or English language to understand the
18
19 222 questionnaires
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24 224 **Outcome measures**

25
26 225 The burn-related injury pattern will serve as primary outcome measure. Information on the
27
28 226 following items, representing injuries and mechanism, will be collected from the patients'
29
30 227 medical files:

31
32 228 - Inhalation injury (yes or no)

33
34 229 - Body regions burned, severity (% TBSA burned as assessed by a trained research
35
36 230 physician)

37
38 231 - Extent of burns (superficial dermal, deep dermal, or subdermal)

39
40 232 - Setting (home, work, or other)

41
42 233 - Burn etiology (scald, flame, contact, chemical, or other)
43

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48 235 The secondary outcome measures are:

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50 236 1) Compliance with EMSB referral criteria (yes or no)

51
52 237 2) Treatment

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54 238 3) Health care use in hospital with associated treatment costs
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239 4) Health-Related Quality of life (EuroQol-5D-3L (EQ-5D-3L))

240 5) Patient and Observer Scar Assessment Scale (POSAS)

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242 The following treatment characteristics will be collected:

243 - Prehospital transport (ambulance, helicopter emergency medical services, or other

244 - Level of trauma care (level 1, 2, or 3)

245 - Required care (ward or Intensive Care Unit)

246 - Resuscitation (amount of fluid <24h after admission)

247 - Intubation (yes or no)

248 - Bronchoscopy (yes or no)

249 - Wound treatment (wound dressing, topical therapy, or other)

250 - Date of the first operation

251 - Escharotomy (yes or no)

252 - Type of operation (split skin grafting, full thickness skin grafting, or excision and
253 primary closure)

254 - % TBSA that needed skin grafting

255 - Expansion of split skin graft (1:1, 1:1.5, 1:3, or 1:6)

256 - Total number of operations

257 - Indication for second, third, and any subsequent operation

258 - Number of outpatient department visits

259 - Date of discharge from hospital

260 - Reconstructive surgery (release/excision with split skin grafting, full thickness grafting,
261 or laps)

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3 263 In order to determine the treatment costs, the use of hospital resources will be collected from
4
5 264 medical files directly. All direct medical costs due to treatment, complications, and events
6
7 265 during follow-up (*e.g.*, ED visit, diagnostic work-up, therapy, events, surgery, admissions,
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9 266 follow-up visits) will be collected. The economic evaluation will be in accordance with the
10
11 267 Dutch guideline and will use cost prices where possible[14]. Medical costs will be calculated
12
13 268 by multiplying the volumes of health care use with the corresponding unit prices.
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18 270 The EQ-5D is a validated questionnaire for measuring health-related quality of life[15, 16].
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20 271 Its use is recommended for the assessment of quality of life in trauma patients, especially for
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22 272 economic assessments[17, 18]. The EQ-5D-3L descriptive system consists of five dimensions
23
24 273 of health (mobility, self-care, usual activities, pain/discomfort anxiety/depression), each with
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26 274 three possible answers. Scores are converted to a utility score ranging from zero to one, with
27
28 275 lower scores indicating poorer quality of life. The EQ Visual Analog Score (VAS) records the
29
30 276 respondents self-rated health status on a vertical (0-100) visual analog scale. Patients aged 16
31
32 277 years or older will be asked to complete the EQ-5D themselves. Pediatric patients (<16 years)
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34 278 will be asked to complete the youth version of the EQ-5D, or their parent(s) will be asked to
35
36 279 complete a proxy version of the EQ-5D youth version.
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41 281 The POSAS v2.0 (www.posas.org)[19] consists of two parts: a Patient Scale and an Observer
42
43 282 Scale, which aim to provide a rating of several measured of scar quality (vascularity,
44
45 283 pigmentation, relief/texture, thickness, pliability, surface area, pain, and itching/pruritus).
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47 284 Patients aged 16 years or older and parents of younger pediatric patients will complete the
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49 285 patient-reported part, a trained observer will complete the observer-reported part.
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54 287 **Other data collected**
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3 288 The following, additional, data will be collected in order to describe the study population,
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5 289 patient characteristics, additional injury characteristics, and burn-related (adverse) events:
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7 290 - Patient characteristics: age, gender, American Society of Anesthesiologists (ASA)
8
9 291 classification, comorbidities (diabetes or other)
10
11 292 - Additional injury characteristics: Injury Severity Score (ISS), Abbreviated Injury Score
12
13 293 (AIS), for all nine anatomical regions as registered in the trauma registry)
14
15 294 - Burn-related (adverse) events: hematoma (yes or no), excessive blood loss (requiring
16
17 295 blood transfusion), wound infection (requiring antibiotic and/or surgical treatment) (yes
18
19 296 or no), pneumonia (yes or no), graft loss requiring surgical intervention (or vac therapy;
20
21 297 yes or no), or other.
22
23 298 - Outcome related variables: duration of hospital admission, time to wound closure
24
25 299 (calculated from date of admission and date of last wound dressing), percentage graft take
26
27 300 5-7 days post burn, discharge destination (home, other hospital, Burn Center,
28
29 301 rehabilitation facility, or other), and mortality (possibly burn-related yes or no)
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303 **Study procedures, data collection methods and participant timelines**

304 Patients will be followed for one year, with visits planned at three weeks (window 2-4
305 weeks), three months (window 11-15 weeks), six months (window 5-7 months), and 12
306 months (window 12-14 months) after admission (Table 2). One additional, optional visit is
307 planned at six weeks (window 5-7 weeks) in case the burn wound has not closed at three
308 weeks. Wound closure is defined as 95% closure, as judged upon wound inspection by the
309 research physician and the local treating physician or specialized wound care nurse. In case of
310 disagreement, consensus will be reached by discussion. The coordinating investigator or
311 research assistant will be present at each outpatient department visit of the enrolled patients
312 for direct collection of data. The study will not interfere with treatment or follow-up.

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3 313 Patient characteristics, injury characteristics, and any other relevant data will be
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5 314 collected from the patient's medical files as soon as possible after signing informed consent.
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7 315 Treatment and other clinical data such as adverse events will be collected (partly from the
8
9 316 patient files) at each follow-up visit. During these regular clinical visits, any radiographs or
10
11 317 digital photos that are routinely obtained will be collected. For the purpose of the study,
12
13 318 additional details concerning treatment and outcome that are not mentioned in the patient's
14
15 319 hospital files, may be registered on the case report forms directly. At the one-year follow-up
16
17 320 visit, the coordinating investigator or research assistant will document any secondary
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19 321 intervention that may be planned for the patient.
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22 322 As soon as possible after inclusion, patients will be asked to complete the EQ-5D-3L
23
24 323 reflecting their pre-injury quality of life. At three months, six months, and at 12 months after
25
26 324 the primary hospital admission, patients (or the parents of pediatric patients) will be asked to
27
28 325 complete the EQ-5D-3L and the patient-reported part of the POSAS. The coordinating
29
30 326 investigator or research assistant will complete the physician-reported part of the POSAS.
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34 328 **Blinding**

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37 329 Patients, the research physician who determines % TBSA, wound closure, and scar quality,
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39 330 and the statistician will not be blinded.
40

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42 332 **Sample size**

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45 333 Given the epidemiologic nature of the primary aim and the lack of information of the
46
47 334 population admitted to a hospital without Burn Center, a formal sample size calculation was
48
49 335 not made. By including all patients treated in the trauma regions South-West Netherlands and
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51 336 Brabant during 18 months, as well as all patients with >10% TBSA burned who are primarily
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53 337 admitted or secondarily referred to a Burn Center, the maximum number of inclusions will be
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55 338 achieved in both cohorts. The larger the number of patients, the more reliable the analysis will
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3 339 be. Enrolling all patients possible will result in the highest reliability of data (*i.e.*, accurate
4
5 340 point estimate with lowest possible variance). Based on the data in the annual report of
6
7 341 Trauma Center South-West Netherland (*i.e.*, 109 patients admitted outside the Burn Center in
8
9 342 the year 2014), we expect to include approximately 300 patients in 18 months in the two
10
11 343 trauma regions combined.

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13 344

14 345 **Statistical analysis**

15
16 346 Data will be analyzed using the Statistical Package for the Social Sciences (SPSS) version
17
18 347 21.0 or higher (SPSS, Chicago, Ill., USA) and will be reported following the Strengthening
19
20 348 the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Missing
21
22 349 values will not be replaced by imputation. Normality of continuous data will be tested with
23
24 350 the Shapiro-Wilk test, and homogeneity of variances will be tested using the Levene's test. A
25
26 351 p-value <0.05 will be taken as threshold of statistical significance in all statistical tests, and all
27
28 352 tests will be two-sided. No interim analysis is planned.

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31 353 First, descriptive analysis will be performed in order to report the outcome measures
32
33 354 and other collected data. Data will be reported for the entire population as well as separately
34
35 355 for the group of patients admitted to a hospital without versus with a Burn Center. For
36
37 356 continuous data (*e.g.*, EQ-5 and POSAS, the mean and SD (parametric data) or the median
38
39 357 and quartiles (non-parametric data) will be reported. The only exception are cost data, these
40
41 358 will be reported as mean with 95% confidence interval (95% CI). The 95% CI around the
42
43 359 mean costs will be approximated by nonparametric bootstrapping. For categorical data (*e.g.*,
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45 360 EMSB compliance), the number and frequencies will be reported.

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48 361 Next univariate analysis will be done in order to compare the two cohorts. Statistical
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50 362 significance of difference between the two groups will be tested using a Student's T-test
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52 363 (parametric, continuous data; with or without equal variance assumed as applicable), Mann-
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3 364 Whitney U-test (non-parametric, continuous data), or Chi-squared or Fisher's Exact test
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5 365 (categorical data, as applicable).
6

7 366 Subgroups will be determined based on the patients included. Relevant subgroups can
8
9 367 be children versus adults versus elderly, subgroups with different percentages TBSA burned,
10
11 368 or patients admitted in compliance versus disagreement with the EMSB referral criteria.
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13 369 Should formal testing between the latter two subgroups be feasible, this will be done as
14
15 370 described above.
16

17 371 The economic evaluation will include costs for health care. Direct and indirect,
18
19 372 medical and non-medical cost will be measured as indicated in the Dutch guidelines for
20
21 373 economic evaluations, using standard, published cost prices where possible[14].
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26 375 **Data management and monitoring**

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28 376 Data will be encoded and stored in a pass-word protected OpenClinica database with
29
30 377 restricted access to the researchers only. Data will be entered once. Quality of the entered data
31
32 378 will be monitored by checking entry for a random sample of patients prior to database
33
34 379 locking.
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37 381 **Patient and public involvement**

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39 382 The need for this study emerged from meetings of the Association of Dutch Burn Centers as
40
41 383 well as the Dutch Burns Foundation, representing both health care professionals and patients.
42
43 384 Input into the design, comparison, and outcome measures was given during presentation for
44
45 385 the Scientific Board of the Dutch Burns Foundation. Patients were not directly involved in the
46
47 386 subsequent writing of the protocol, nor were they directly involved in the recruitment to and
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49 387 conduct of the study. A summary of the main results will be made available to study
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51 388 participants on request.
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390 **Ethics and dissemination**

391 This study will be conducted according to the principles of the Declaration of Helsinki (64th
392 World Medical Association General Assembly, Fortaleza, Brazil, October 2013).

393 This study has been exempted by the medical research ethics committee (MREC)
394 Erasmus MC (Rotterdam, The Netherlands). This MREC acts as central ethics committee for
395 this trial (reference number MEC-2017-356). Approval has been obtained from the local
396 hospital boards in all participating centers. Following review of the protocol (version 1.0 date
397 22-may-2017, the MREC concluded that this study is not subject to the Medical Research
398 Involving Human Subjects Act (WMO). They concluded that the study is a medical/scientific
399 research, but no patients are subjected to procedures or are required to follow rules of
400 behavior. Consequently, the statutory obligation to provide insurance for subjects
401 participating in medical research (article 7 of the WMO) does not apply. Any important
402 changes in the protocol will be submitted to the accredited MREC. The results of the study
403 are planned to be published in an international, peer reviewed journal and presented at
404 national and international trauma and burn care meetings. Each participating center will
405 provide a group author to every publication. No personal data of study participants will be
406 presented.

407

408 Discussion

409 Burns cause significant morbidity and mortality worldwide, and depending on the severity,
410 burn injuries may require specialized burn care in a dedicated Burn Centers. In order to enable
411 optimal triaging and referral to a Burn Center, the EMSB referral criteria have been
412 implemented[10]. Whereas extensive injury and outcome registration exists for patients
413 admitted to a dedicated Burn Center, there are currently no data available that provide
414 sufficient details about patients admitted to a hospital without Burn Center. Successful
415 completion of this study will provide more insight into the percentage of patients admitted to
416 a hospital without dedicated Burn Center. It will also provide us detailed data on patient and
417 injury characteristics, EMSB compliance, treatment, treatment costs, relevant outcome data,
418 and quality of life of burn patients with primary admission at a hospital without Burn Center
419 as well as patients with <10% TBSA burned who are secondarily referred to a Burn Center.
420 Twenty-one hospitals will participate. Although the participation of multiple hospitals may
421 introduce treatment bias, it also makes the results more generalizable.

422

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For peer review only

475 **List of abbreviations used**

476 AIS, Abbreviated Injury Scale; ASA classification, American Society of Anesthesiologists
477 classification; 95%CI, 95% Confidence Interval; DBR R3, Dutch Burn Repository R3; ED,
478 Emergency Department; EMSB, The Emergency Management of Severe Burns; EQ-5D,
479 EuroQoL-5D; ISS, Injury Severity Score; LIS, Letsel Informatie Systeem (in English:
480 National Injury Surveillance System); LMR, Landelijke Medische Registratie (in English:
481 National Medical Registration); LNAZ, Landelijke Netwerk Acute Zorg (in English: National
482 Network Acute Care); LTR, Landelijke Trauma Registratie (in English: National Trauma
483 Registry); MEC, Medisch Ethische Commissie (in English: Medical Research Ethics
484 Committee (MREC); NTR, Nederlands Trial Register (in English; Netherlands National Trial
485 Register); POSAS, Patient and Observer Scar Assessment Scale; QoL, Quality of Life; SD,
486 Standard Deviation; SPSS, Statistical Package for the Social Sciences; STROBE,
487 STrengthening the Reporting of OBServational studies in Epidemiology; TBSA, Total Body
488 Surface Area; VAS, Visual Analog Scale; WMO, Medical Research Involving Human
489 Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen).

490

491 **Competing interests**

492 The authors declare that they have no competing interests.

493

494 **Authors' contributions**

495 EMMVL, DTVY, MEVB, SP, MHJV, and CHVDV developed the study. MHJV will act as
496 trial principal investigator. DTVY, DB, AYMVPC, PARDR, MG, TMALK, KWWL, ANR,
497 MS, LVDS, AHVDV, FCVE, PVVE, PAV, DIV, MW, MHJV, and CHVDV will participate
498 in patient inclusion and outcome assessment. DTVY, SP, and EMMVL will perform

1
2
3 499 statistical analysis of the study data. DTVY and EMMVL drafted the current manuscript. All
4
5 500 other authors have read and approved this final manuscript. At the end of the study, DTVY
6
7 501 and EMMVL will draft the manuscript. All other authors will interpret the data, critically
8
9 502 revise the manuscript, and approve the final version to be submitted.
10

11 503

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14
15
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17
18 506 Netherlands; reference number WO/16.110). The funder of the study has no role in study
19
20 507 design, data collection, data analysis, data interpretation, or writing of the report.
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24 25 509 **Competing interests statement**

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28 510 The authors declare that they have no competing interests.
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511 **Tables**512 **Table 1: EMSB referral criteria**[10]

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- 1) The percentage Total Body Surface Area burned (TBSA burned; >10% TBSA in adults or >5% in children)
 - 2) Burns of special areas (face, hands, feet, perineum, genitalia, and major joints)
 - 3) Full thickness burns >5% TBSA burned
 - 4) Electrical burns
 - 5) Chemical burns
 - 6) Burns with associated inhalation injury
 - 7) Circumferential burns of limbs or chest
 - 8) Extremes of age (children and elderly)
 - 9) Pre-existing medical disorders which could complicate management and prolong recovery or effect mortality
 - 10) Associated trauma
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513

514 **Table 2: Schedule of events**

Event forms	Screening	3 we (2-4 we)	6 we* (5-7 we)	3 mo (11-15 we)	6 mo (6-7 mo)	12 mo (12-14 mo)
Screening	X					
Informed Consent		X				
Patient characteristics		X				
Injury characteristics		X				
Radiology		X ¹	X ¹	X ¹	X ¹	X ¹
Digital photo		X ¹	X ¹	X ¹	X ¹	X ¹
Treatment characteristics		X	X	X	X	X
Outcome details		X	X	X	X	X
Adverse Events		X	X	X	X	X
Clinical FU		X	X	X	X	X
Health Care Consumption		X	X	X	X	X
EQ-5D		X ²		X	X	X
POSAS				X	X	X
Early withdrawal		**	**	**	**	**

515 *Optional visit; will only take place if wounds are not closed at three weeks.

516 ¹Only if treating surgeon requests these images.517 ²Asking for EQ-5D pre-burn.

518 ** Only at time of withdrawal.

STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	4-5
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7-9
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9, 14-15
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-11, 14
		(b) For matched studies, give matching criteria and number of exposed and unexposed	N.A.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-14
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	11-14
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	15-16
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	16
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	16-17
		(b) Describe any methods used to examine subgroups and interactions	17
		(c) Explain how missing data were addressed	16
		(d) If applicable, explain how loss to follow-up was addressed	16
		(e) Describe any sensitivity analyses	N.A.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N.A.
		(b) Give reasons for non-participation at each stage	N.A.
		(c) Consider use of a flow diagram	N.A.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	N.A.
		(b) Indicate number of participants with missing data for each variable of interest	N.A.
		(c) Summarise follow-up time (eg, average and total amount)	N.A.
Outcome data	15*	Report numbers of outcome events or summary measures over time	N.A.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	N.A.

		(b) Report category boundaries when continuous variables were categorized	N.A.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N.A.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	N.A.
Discussion			
Key results	18	Summarise key results with reference to study objectives	N.A.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N.A.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	19
Generalisability	21	Discuss the generalisability (external validity) of the study results	19
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	23

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.