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Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial

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Complete List of Authors:	<p>Vrbica, Kamil; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine</p> <p>Hudec, Jan; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine</p> <p>Hrdy, Ondrej; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine</p> <p>Galko, Michal; University Hospital Brno, Department of Orthopaedic Surgery; Masaryk University Faculty of Medicine, Department of Orthopaedic Surgery</p> <p>Horalkova, Hana; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine</p> <p>Demlova, Regina; Masaryk University Faculty of Medicine, Department of Pharmacology/CZECRIN</p> <p>Kubelova, Michaela; Masaryk University Faculty of Medicine, Department of Pharmacology/CZECRIN</p> <p>Repko, Martin; University Hospital Brno, Department of Orthopaedic Surgery; Masaryk University Faculty of Medicine, Department of Orthopaedic Surgery</p> <p>Gal, Roman; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine</p>
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Manuscripts

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4 1 **Effect of Prophylactic Fibrinogen Concentrate In Scoliosis**
5 2 **Surgery (EFISS): a study protocol of two-arm, randomised trial**
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8 4 Vrbica K¹, Hudec J¹, Hrdy O¹, Galko M³, Horalkova H¹, Demlova R⁴, Kubelova M⁴,
9 5 Repko M³, Gal R¹
10 6

11 7
12 8 1) Department of Anaesthesiology and Intensive Care Medicine, University
13 9 Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech
14 10 Republic

15 11 2) Department of Orthopaedic Surgery, University Hospital Brno and Faculty of
16 12 Medicine, Masaryk University, Brno, Czech Republic

17 13 3) Department of Pharmacology/CZECRIN, Faculty of Medicine, Masaryk
18 14 University, Brno, Czech Republic

19 15 **Correspondence to:** Jan Hudec, hudeja@gmail.com, University Hospital Brno and
20 16 Faculty of Medicine, Masaryk University, Brno, Jihlavská 20, 625 00 Brno, Czech
21 17 Republic

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39 **Abstract**

41 **Introduction**

42 Fibrinogen is one of the essential coagulation factors. Preoperative lower
43 plasma fibrinogen level has been associated with higher blood loss. Scoliosis
44 surgery presents a challenge for the anaesthetic team, one of the reasons being
45 blood loss and transfusion management. Recently, the prophylactic fibrinogen
46 administration has been a debated topic in various indications. It has been described
47 e.g. in urological or cardiovascular surgery, as well as in paediatrics. This pilot study
48 is focused on verifying the feasibility of potential large randomised trial and verifying
49 the safety of prophylactic fibrinogen administration in paediatric scoliosis surgery.

50 **Methods and analysis**

51 A total of 32 paediatric patients indicated for scoliosis surgery will be
52 recruited. Participants will be randomised into study groups in a 1:1 allocation ratio.
53 Patients in the intervention group will receive prophylactic single dose of fibrinogen,
54 in addition to standard of care. Patients in the control group will receive standard of
55 care without study medication prior to skin incision. The primary aim is to assess the
56 safety of prophylactic fibrinogen administration during scoliosis surgery in children,
57 the incidence of any adverse events (AEs) and reactions will be monitored during
58 participation in the study. The secondary objective is to investigate the additional
59 safety information, feasibility and efficacy of a prophylactic fibrinogen administration.
60 The incidence of AEs and reactions according to selected Adverse Events of Special
61 Interest will be monitored. All collected data will be subjected to statistical analysis
62 according to a separate Statistical Analysis Plan.

63 **Ethics and dissemination**

64 This trial follows the applicable legislation and requirements for good clinical
65 practice according to the ICH E6(R2). All essential trial documents were approved by
66 the relevant ethics committee and national regulatory authority (State Institute for
67 Drug Control) and their potential amendments will be submitted for approval.

68 **Trial registration number and protocol version**

69 ClinicalTrials.gov Identifier: NCT05391412
70 EudraCT No.: 2021-005493-25. Protocol version is 1.1 of the date 28/2/2022.

73 **Key words**

74 scoliosis, fibrinogen, paediatrics, orthopaedic, anaesthesiology

76 **Strength and limitations of the study**

- 77 1. Results of this study might improve knowledge about prophylactic fibrinogen
78 administration in the paediatric population during scoliosis surgery.
- 79 2. The results of this feasibility study will provide data to plan a fully powered
80 randomised trial.

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81 3. Results of this study might support the claim about the safety of the fibrinogen
82 administration before surgery.

84 4. The participants are younger than 18 years at the time of recruitment,
85 according to national legislation, the informed consent must be signed by both
86 parents or legal guardians.

87 5. The feasibility assessment may indicate a lack of data to determine the
88 influence on blood loss and bleeding management.

For peer review only

124 **Background**

125 Scoliosis is defined as an abnormal lateral deviation of the spine of more than
126 10° in the frontal plane, with deviation in the sagittal plane and vertebral rotation. It is
127 one of the most common spinal deformities in children (1–3). The approach to the
128 treatment is multidisciplinary and depends on the scoliotic curve severity and
129 progression (4). The surgery is commonly indicated in patients with progressive
130 curves and Cobb angle over 40° to stop further progression of the curve and prevent
131 the development of multiple organ disease (5). Except for musculoskeletal disorders,
132 cardiovascular, respiratory, gastrointestinal, or psychosocial problems are described
133 in patients with scoliosis (6). Anaesthesia for scoliosis surgery is a highly challenging
134 task for the whole team. The specifics of such anaesthesia include e.g. long
135 operation time, body temperature decrease, high blood losses, positioning, or
136 intraoperative neurophysiological monitoring (7,8).

137 During scoliosis surgery, high blood loss and the necessity of blood
138 transfusions are described, while allogeneic derivatives are necessary in the
139 perioperative period in about 30 % to 60 % of cases (9). Bleeding complications and
140 adverse events associated with blood transfusions prolong and increase the cost of
141 hospitalisation and increase the mortality (10). Well-known and commonly applied
142 approaches to reduce blood loss include antifibrinolytics, such as tranexamic acid,
143 which can be administered before surgery (11,12), permissive hypotension, which
144 can be used to reduce blood loss. Prevention of hypothermia is another way to
145 reduce bleeding, and cell salvage, especially in high-risk patients, where it is
146 preferred to minimise allogeneic blood transfusions (13).

147 Fibrinogen is essential for clot formation and stopping bleeding (14,15).
148 Hypofibrinogenemia or dysfibrinogenemia leads to more severe bleeding during
149 high-extensive surgery (16–18). Moreover, some studies describe less blood loss in
150 patients with higher preoperative fibrinogen levels (19). Prophylactic administration
151 of fibrinogen is a widely discussed theme, but to date, the data are limited (20).
152 Some studies described a significant reduction in blood loss and a secondary
153 reduction in allogeneic derivatives administration. Prophylactic fibrinogen
154 administration has been described in cardiovascular or urological surgery (21–23).
155 Additionally, early administration has been reported to be safe in the paediatric
156 population (24).

157 However, the effect of prophylactic fibrinogen administration in paediatric
158 scoliosis surgery remains unclear. We designed this study to verify the feasibility of
159 prophylactic fibrinogen administration in paediatric scoliosis surgery. The results will
160 be used to plan a sufficiently large randomised trial with the aim to clarify the impact
161 of prophylactic fibrinogen application on the magnitude of blood loss and the need
162 for transfusion. This study is focused on the safety, efficacy, and feasibility of
163 prophylactic administration of fibrinogen in scoliosis surgery. The clinical outcome of
164 each participant is studied, particularly the incidence of potential adverse events
165 such as thromboembolism, allergic reactions, or fevers. The results of this study may

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3 166 improve knowledge about prophylactic fibrinogen application. All participants in this
4 167 study will contribute to this socially beneficial knowledge.
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7 169 **Methods and analysis**

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10 171 **Study design**

11 172 The setting of the study is two-arm, prospective, monocentric, randomised,
12 173 double-blind pilot trial with a 1:1 allocation ratio testing safety, efficacy and feasibility
13 174 of prophylactic fibrinogen administration during scoliosis surgery in the paediatric
14 175 population. The pilot study started on 1/6/2022. The study protocol is compiled
15 176 according to the SPIRIT (Standard Protocol Items: Recommendations for
16 177 Interventional Trials) checklist (25).
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19 179 **Aims and objectives**

20
21 180 This pilot study is conducted before designing a fully powered study. It aims to
22 181 assess the safety, feasibility, and efficacy of prophylactic fibrinogen administration
23 182 during scoliosis surgery in the paediatric population. Results from this pilot study will
24 183 be used to optimise the study design and power analysis to determine the sample
25 184 size of the final study.

26 185 The primary aim of a clinical trial is to assess the safety of perioperative
27 186 infusion of fibrinogen during scoliosis surgery in children. The incidence of any
28 187 adverse events (AEs) and reactions will be monitored during participation in the
29 188 study.

30 189 The secondary aim is to investigate the additional safety information,
31 190 feasibility and efficacy of a prophylactic administration of fibrinogen. The incidence of
32 191 adverse events and reactions according to the following Adverse Events of Special
33 192 Interest (AESI) will be monitored. Monitored AESI include deep vein thrombosis
34 193 verified on ultrasound imaging, pulmonary embolism confirmed on CT scan, and
35 194 infection or healing disorder requiring re-surgery and/or the initiation of antibiotic
36 195 therapy.

37 196 Other endpoints and monitored parameters, such as additional safety
38 197 information, demographic characteristics, laboratory values, comparison of blood
39 198 loss, or feasibility assessment, are mentioned in the section "Data collection."
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41 199

42 200 **Participants**

43 201 *Eligibility criteria*

44 202 All patients admitted to the hospital for scoliosis surgery will be screened for
45 203 inclusion criteria. When inclusion criteria will be met, the exclusion criteria will be
46 204 checked. Only patients with fulfilled all inclusion criteria and without all exclusion
47 205 criteria will be considered for participation in the study.
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50 207 *Inclusion criteria are as follows:*

- 51 208 - Elective scoliosis surgery.
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3 209 - Age < 18 years at the time of enrollment.
4 210 - Signed the relevant informed consent form.
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6 211 - Sexually active participants (≥ 15 years old) must agree to the use of following
7
8 212 methods of contraception for the duration of this clinical trial:
9
10 213 - Women - proper use of a highly reliable method of contraception, i.e.
11 214 combined hormonal contraception (oral, vaginal or transdermal form),
12 215 gestagen hormonal contraceptives associated with ovulation inhibition
13 216 (oral or injectable form) or sexual abstinence.
14
15 217 - Men - sexual abstinence or the use of an adequate contraceptive
16 218 method (i.e. condom) in case of sexual intercourse.

17
18 219 *Exclusion criteria are as follows:*

- 19 220 - Diagnosed congenital or acquired coagulopathy.
20 221 - Use of anticoagulants with the exception of perioperative prophylactic
21 222 administration of low-molecular-weight-heparin (LMWH) to prevent venous
22 223 thromboembolism (VTE).
23
24 224 - Known hypersensitivity to the active substance or to any of the excipients of
25 225 Investigational Medicinal Product (IMP).
26
27 226 - History of deep vein thrombosis or pulmonary embolism.
28
29 227 - Pregnancy and lactation.
30

31 228
32 229 **Recruitment and withdrawal**

33 230 The study is conducted at University Hospital Brno, Czech Republic, in
34 231 cooperation with the Department of Anaesthesiology and Intensive Care Medicine
35 232 and the Department of Orthopaedic Surgery. The study is controlled by research
36 233 infrastructure CZECRIN. All patients eligible for the study and the patient's parents/
37 234 legal guardians will be asked to participate in the EFISS study. The informed consent
38 235 has to be signed by both parents or legal guardians. For patients who reach the age
39 236 of 12 at the time of enrollment, adapted written information and an informed consent
40 237 is prepared considering the level of knowledge and the age of patients. All
41 238 participants or their parents / legal guardians can withdraw at any time without giving
42 239 any reason, but they must notify the investigator.
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46 240
47 241 **Sample size**

48 242 Since this is a pilot study, a power calculation to determine sample size is not
49 243 required. Thirty participants (15 in both arms) were defined as a sample size
50 244 according to standard guidelines for pilot studies (26–28). Considering a 5% dropout
51 245 rate, 32 participants will be recruited.
52
53

54 246
55 247 **Randomisation and blinding**

56 248 Patients will be randomised in a 1:1 ratio to receive fibrinogen or standard of
57 249 care without further study medication. Randomisation will be performed electronically
58 250 in the electronic case report form (eCRF) REDCap database by an unblinded
59 251 person.
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3 252 The study medication will be prepared by the unblinded study nurse outside
4 253 the operating theatre. It will be administered after induction of anaesthesia before the
5 254 beginning of surgery under the supervision of an unblinded investigator. The study
6 255 nurse and investigator will be unblinded for the duration of this study and will not be
7 256 part of the operating team. The blinded operating team (orthopaedist,
8 257 anaesthesiologist, and anaesthesiology nurse) will be outside the theatre during the
9 258 IMP application / non-application. After IMP application/ non-application, unblinded
10 259 study nurse and unblinded investigator will leave the operating room, and the blinded
11 260 operating team will enter back to the theatre.

12 261 The data management group and statisticians will work with a pseudo-
13 262 anonymised data set. Emergency unblinding before the end of the study should
14 263 occur only in exceptional circumstances when knowledge of the actual treatment is
15 264 necessary for further management of the patient's treatment. This activity can be
16 265 performed directly in the REDCap electronic database. The investigator must report
17 266 all unblindings (with reason) as they occur on the corresponding eCRF page.

18 267

19 268 **Intervention**

20 269 *Choice of comparators*

21 270 Bleeding and coagulopathy are present during scoliosis surgery, and lack of
22 271 fibrinogen plays a crucial role in it. We decided to reduce blood loss and
23 272 coagulopathy development, the fibrinogen will be administered preventively in the
24 273 intervention arm. The standard of care is to wait for current blood loss or blood count
25 274 and coagulation values during surgery before administration of blood products. This
26 275 standard approach will be compared with the intervention.

27 276 *Standard of care*

28 277 All study participants will receive standard of care in blood and coagulation
29 278 management for scoliosis surgery. Blood tests including haemoglobin (Hb),
30 279 hematocrit (Htc), platelet count (Plt), fibrinogen level (Fbg), activated partial thrombin
31 280 time (aPTT), prothrombin time (PT), and thrombin time (TT) will be performed before
32 281 the surgery. Values will be checked before surgery, and in case of significant
33 282 pathology, the blood transfusions or plasma derivatives will be administered, or the
34 283 surgery will be delayed. Tranexamic acid will be administered to all patients before
35 284 the skin incision in a dose of 10-15 mg/kg. The standard of care includes the
36 285 restrictive administration of blood transfusion, plasma derivative, and fluids during
37 286 the perioperative period. The anesthesiologist or attending physician in the ICU will
38 287 administer fluids, blood transfusions, and derivatives depending on clinical
39 288 judgement, blood loss, blood count, coagulation tests, and vital signs. The goals
40 289 during bleeding are haemoglobin 7-9 g/dL, fibrinogen above 2 g/L, platelets above
41 290 $100 \times 10^9/L$ and normalisation of coagulation status. The administration respects
42 291 international guidelines (29).

43 292 *Intervention description*

44 293 Participants in the intervention group will receive the standard of care, and in
45 294 addition, a single dose of fibrinogen prior to the skin incision. IMP is administered
46 295 intravenously and is immediately available at a plasma concentration corresponding

296 to the dose. It is in a powder form in a vial, and it is necessary to solve this powder
297 carefully. The reconstitution procedure should follow the instructions in the package
298 leaflet. Patients in the intervention group will receive a single dose of IMP
299 intravenously, 20–30 mg/kg (depending on body weight and clinical condition,
300 according to the package leaflet). The medicinal product will be diluted in a 100 ml
301 infusion bag and will be administered after induction to anaesthesia before surgery.
302 The infusion rate should not exceed approximately 5 ml per minute. The IMP will be
303 administered according to the above study blinding rules.

304 305 **Comparison**

306 Participants in the intervention group will receive standard of care and IMP
307 before skin incision. Participants in the control group will receive standard of care
308 without study medication before skin incision. The blinded operating team will
309 manage both groups according to the standard of care after the initial
310 intervention/non-intervention. Therefore, fibrinogen can be administered to all
311 patients if indicated during surgery or in the postoperative period.

312 Primary and secondary outcomes will be compared between intervention and
313 control groups to assess the potential feasibility of a large-scale study.

314 315 **Trial feasibility**

316 The trial feasibility assessment is one of the secondary aims of this study. We
317 will monitor the recruitment rate of eligible patients who will be approached for
318 consent to participate. The feasibility criterion is more than 75 % of enrolled
319 participants. We will also evaluate the percentage of missing outcomes and clinical
320 data. The goal is to have less than 10 % missing outcome data, including ICU and
321 hospital length of stay (LOS) and survival, and less than 10% missing clinical data
322 obtained from clinical medical notes and electronic patient records.

323 324 **Clinical outcomes**

325 The clinical outcome focuses on reducing blood loss and transfusions in
326 paediatric patients after prophylactic fibrinogen administration during scoliosis
327 surgery. Blood loss and plasma derivatives management will be reported for each
328 participant. Blood count and coagulation parameters will be monitored before
329 surgery, in the end, and 24 hours after the surgery. All parameters will be recorded in
330 the eCRF database.

331 332 **Data collection**

333 During the course of the trial, subjects will be monitored during hospitalisation
334 and after discharge. According to medical records, all data will be collected in an
335 eCRF. Data of blood count (Hb, Hct, Plt) and coagulation status (PT, aPTT, TT, Fbg)
336 will be filled in eCRF before surgery, after surgery, and 24 hours after surgery.
337 Information about inclusion and exclusion criteria, informed consent, and
338 demographic data will be obtained on the day of enrollment. Collected participant
339 demographic data will be age (years), sex (male, female), and weight (kilograms).

340 Blood samples will be taken before surgery according to standard of care, post-
 341 operative blood samples will be taken immediately after surgery and 24 h after
 342 surgery. We will record blood loss, the volume of blood loss for the surgical segment
 343 of the spine, and urinary output during surgery and 24 hours after surgery. We will
 344 track the number, type, and volume of administered transfusion products, plasma
 345 derivatives, crystalloid solutions, and colloid solutions during surgery and in 24 hours
 346 postoperative period. The critical part of monitored data will be the incidence of
 347 adverse events and reactions according to the following AESI. These reactions will
 348 include deep-vein thrombosis verified on ultrasound imaging, pulmonary embolism
 349 confirmed on CT, infection or healing disorder requiring re-surgery, and/or the
 350 initiation of antibiotic therapy.

351 Other monitored additional safety information will be:

- 352 - Hospital LOS.
- 353 - Intensive care length of stay (ICU LOS) (day of admission and day of
 354 discharge will be counted as one day).
- 355 - 28-day mortality (number of patients who are not alive 28 days after
 356 randomization).

357 According to the SPIRIT checklist the schedule of enrollment, interventions, and
 358 assessments is summarised in Table 1 (25).

360 **Table 1:** Clinical trial schedule

	STUDY PERIOD						
	Screenin g	Allocatio n	Post-allocation		Hospital discharg e	Follow- up	Premature termination
TIMEPOINT	D_0	D_{0-1}	D_1	D_2	D_{3-28}	D_{28}	Anytime
ENROLMENT:							
Inclusion/Exclusion criteria	X						
Informed consent	X						
Pregnancy testing ¹	X						
Randomization		X					
INTERVENTION:							
Study medication application ²			X				
ASSESSMENTS:							
Demographic data ³	X						
Adverse events			X	X	X	X	X
Laboratory testing ⁴			X	X			
Blood loss ⁵			X	X			
Urinary output ⁶			X	X			
Transfusion products consumption ⁷			X	X			
Fluid therapy ⁷			X	X			
ICU LOS (days)					X		
LOS (days)					X		
28-day mortality						X	
Reason for premature termination							X

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2
3 362 1 urine pregnancy testing
4 363 2 fibrinogen infusion or standard of care
5 364 3 age, sex, weight
6 365 4 haemoglobin, haematocrit, platelet count, fibrinogen, aPTT, PT, TT
7 366 5 volume (ml) during surgery and in the 24-hour postoperative period and volume (ml) related to the surgical
8 367 segment of the spine
9 368 6 volume (ml) in the 24-hour postoperative period
10 369 7 type and volume (ml) during surgery and in the 24-hour postoperative period
11 370

11 371 All study-related information will be stored securely at the study site. All
12 372 participant information will be stored in locked file cabinets in areas with limited
13 373 access. All local databases will be secured with password-protected access
14 374 systems. Forms, lists, logbooks, appointment books, and other listings that link
15 375 participant ID numbers to additional identifying information will be stored in a locked
16 376 file in an area with limited access. No later than 3 years after the collection of the 1-
17 377 year post-randomization, we will deliver a completely blinded data set to an
18 378 appropriate data repository for sharing purposes. Statistical codes will be archived in
19 379 accordance with SOPs.
20 380

21 381 **Statistical analysis**

22 382 A separate Statistical Analysis Plan (SAP) will be prepared to provide details
23 383 on the approach to analyses. The SAP will be finalised before the database lock. All
24 384 eventual deviations from the SAP will be described and justified in the relevant part
25 385 of the Clinical Trial Report. As a general approach for the descriptive analysis, the
26 386 following statistics will be provided for continuous variables: the number of subjects
27 387 with available data (n), mean, standard deviation, median, minimum and maximum.
28 388 The number and percentage of patients will be provided for categorical variables. For
29 389 a comparison of continuous variables between treatment groups two-sample t-test or
30 390 its nonparametric alternative Mann-Whitney test will be used, where appropriate.
31 391 Pearson's chi-square test or Fisher exact test will be used to compare categorical
32 392 variables, where appropriate. All statistical tests will be two-sided. P-values < 0.05
33 393 will constitute statistically significant differences. During the pilot study the interim
34 394 analysis is not planned.

35 395 Protocol non-adherence will be assessed by the principal investigator case by
36 396 case. Patients with major deviations from the study protocol will be excluded from
37 397 the analysis. Missing data are not planned to be imputed. However, in the event of
38 398 substantial missing data for any parameter, a sensitivity analysis using any method
39 399 of imputation could also be used.

40 400 **Patient and public involvement**

41 401 Patients or the public will not be involved in the study development. This
42 402 EFISS study was proposed and designed by an expert team of University Hospital
43 403 Brno and the Faculty of Medicine, Masaryk University Brno in the Czech Republic.
44 404

45 405 **Monitoring and auditing**

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3 406 The trial centre will be monitored according to the monitoring plan provided by
4 407 research infrastructure CZECRIN. The objectives of the monitoring are to ensure that
5 408 the trial participant's safety and rights are respected, that accurate, valid and
6 409 complete data are collected, and that the trial is conducted in accordance with the
7 410 trial protocol, the principles of GCP and national legislation. Sponsor, Regulatory
8 411 authority and Ethics committees have the right to inspect/audit the trial site.
9 412

12 413 **Ethics and dissemination**

14 414 This trial follows the applicable legislation and requirements for good clinical
15 415 practice according to the ICH E6(R2). Compliance with this standard provides public
16 416 assurance that the rights, safety, and well-being of trial participants are protected
17 417 and that the clinical trial data are credible.

19 418 All essential trial documents were approved by the relevant ethics committee
20 419 and national regulatory authority (State Institute for Drug Control) and their potential
21 420 amendments will be submitted for approval. The study was approved by University
22 421 hospital Brno's Ethics Committee (No.: 24/22MONO) and by State Institute for Drug
23 422 Control (No.: sukls11048/2022). This clinical study includes patients belonging to the
24 423 category of vulnerable subjects, namely children and adolescents under 18 years of
25 424 age.

28 425 *Informed consent procedure*

30 426 The parents / legal guardians will receive written information and an informed
31 427 consent form (ICF). The investigator will inform in a comprehensible manner about
32 428 the nature, purpose, and significance of the clinical trial simultaneously. This
33 429 procedure will take place before enrolling the child in the study. Parents / legal
34 430 guardians will also be informed of the measures to protect personal data. That
35 431 liability insurance has been arranged for investigators and sponsors in the event of
36 432 health damage due to a clinical trial, including possible compensation for trial
37 433 subjects. Paediatric patients will receive from the investigator information on the
38 434 clinical trial adapted to their level of knowledge and intellectual abilities, including
39 435 details on the benefits and risks of participating in this clinical trial. The explicit wish
40 436 of instructed paediatric patients to refuse to participate or to withdraw from a clinical
41 437 trial at any time is always respected. Written information and an informed assent
42 438 form are prepared for patients who reach the age of 12 at the time of enrollment.
43 439 Paediatric patients and their parents / legal guardians will get sufficient time to study
44 440 the written information and the informed consent form carefully and will ask
45 441 additional questions to which the investigator must respond satisfactorily. All legal
46 442 representatives (both parents) will must sign the informed consent form at the end of
47 443 the process.

53 444 *Supervision of the informed consent procedure*

55 445 The process of obtaining informed consent from the patient's parents / legal
56 446 guardians, or patients, must always be adequately documented by the investigator
57 447 using valid forms and the patient's medical records. The clinical trial monitor will
58 448 check the process during monitoring visits. Significant deviations in the process will
59 449 lead to the termination of the patient's participation in the trial.

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3 450**451 Discussion**

452 Prophylactic fibrinogen administration before high-risk surgeries is a widely
453 discussed topic across medical fields. Preoperative lower levels of fibrinogen are
454 associated with higher blood loss in adolescent idiopathic scoliosis surgery.
455 However, if the effect of prophylactic fibrinogen administration will lead to blood loss
456 reduction in these patients is unclear (17,18,30).

457 The safety of fibrinogen administration in the paediatric population has been
458 demonstrated in several studies (24,31). However, in these studies, fibrinogen was
459 substituted during the surgery according to the viscoelastic haemostatic assays, the
460 substitution was not prophylactic. In addition, the number of participants was low. In
461 summary, data on prophylactic administration in children and adolescents are
462 insufficient, more studies are needed.

463 We can see some similarity with tranexamic acid administration. In recent
464 years, tranexamic acid has been commonly used in scoliosis surgery to reduce blood
465 loss (32–34). The efficacy of tranexamic acid is unambiguous, it reduces blood loss,
466 the need for blood transfusions and the length of hospitalisation (32). The use of
467 tranexamic acid is incorporated in orthopaedic recommendations for blood
468 management (35). However, some studies have provided evidence of the
469 thromboembolic potential of tranexamic acid (36,37). In contrast, fibrinogen is not
470 associated with higher thromboembolic risk repeatedly (38). It is appropriate to study
471 fibrinogen concentrate to see if it has the same positive properties as tranexamic
472 acid without possible side effects.

473 This pilot study also has some limitations. The sample size is designed
474 according to standard guidelines for pilot studies, so it is limited to 32 patients.
475 Participants are under the age of 18, so informed consent has to be signed by both
476 parents or legal guardians, which may lead to limited enrollment. Data are collected
477 28 days after randomisation, which may not be an adequate interval to evaluate
478 safety and feasibility. And final limitation is the absence of placebo administration in
479 the standard of care group. This absence is mainly caused by the requirements of
480 the national regulatory authority, which does not allow the administration of a
481 placebo without a therapeutic or preventive effect in the paediatric population.

482

483 Conclusion

484 This pilot study should demonstrate the safety and feasibility of the intended
485 intervention and form the basis for a later large study which could have extensive
486 impact in scoliosis surgery and bleeding management. But the results will not prove
487 most likely the efficacy of prophylactic administration of fibrinogen in scoliosis
488 surgery.

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492 Acknowledgements

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3 493 The authors thank everyone involved in the study, concretely the participants,
4 494 assessors and all health care providers taking care for participants.
5 495

6 496 **Contributions**

7
8 497 OH, RG first conceived this protocol after revision from the other authors. KV,
9 498 JH, MG are the main authors and editors of this manuscript. MG, MR are responsible
10 499 for patient involvement. JH, KV, HH provide standards of care. CZECRIN (MK, RD)
11 500 assisted in the development of the study protocol and is responsible for statistical
12 501 analysis. All authors read and approved the final version of the manuscript.
13 502

14 503 **Sponsor**

15 504 Name and contact information for the trial sponsor:

16 505 Trial Sponsor: Masaryk University Brno

17 506 Contact name: prof. Martin Smrcka, MD, PhD, MBA

18 507 Address: Jihlavská 20, 602 00 Brno

19 508 Telephone: +420532232884

20 509 Email: smrcka.martin@fnbrno.cz

21 510
22 511 The sponsor has no role in the design of this trial and will not have any role during its
23 512 execution, analyses, interpretation of the data, or the decision to submit results.
24 513

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28 517 development of research organisation (FNBr, 65269705). The project was supported
29 518 by the national budget through MEYS, RI CZECRIN (LM2018128).
30 519

31 520 **Conflict of interest**

32 521 In the past 5 years, KV and RG have received honoraria for lecturing from
33 522 CSL Behring.
34 523

35 524 **Plan**

36 525 We intend to submit the results of the study to be published in a peer-reviewed
37 526 international medical journal. The author team will not change.
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For peer review only



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – <i>lines 1-2</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – <i>lines 68-70</i>
	2b	All items from the World Health Organization Trial Registration Data Set - <i>lines 68-69</i>
Protocol version	3	Date and version identifier – <i>line 70</i>
Funding	4	Sources and types of financial, material, and other support <i>lines 500 - 504</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – <i>lines 4 – 13 and 482 - 487</i>
	5b	Name and contact information for the trial sponsor – <i>lines 489 - 495</i>
	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 - <i>lines 497 - 498</i>
	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) <i>lines 392 - 398</i>
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 - <i>lines 137 - 167</i>
	6b	Explanation for choice of comparators - <i>lines 305 – 313</i>
Objectives	7	Specific objectives or hypotheses - <i>lines 179 - 198</i>

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2	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) - <i>lines 171 - 177</i>
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8	Methods: Participants, interventions, and outcomes		
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10	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 – <i>lines 172 - 173, 492 - 496</i>
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14	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) - <i>lines 200 - 227</i>
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19	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered – <i>lines 268 - 303</i>
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22		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) – <i>line 186 – 195, 237 – 239, 383 – 387</i>
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28		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) – <i>N/A</i>
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32		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial – <i>lines 276 - 291</i>
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35	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 - <i>lines 179 – 198, 324 - 367</i>
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43	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) – <i>Figure 1</i> .
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48	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 – <i>lines 241 - 245</i>
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54	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size – <i>229 – 234</i>
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57	Methods: Assignment of interventions (for controlled trials)		
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59	Allocation:		
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions – <i>lines 247 - 251</i>
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10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned – <i>lines 249 - 251</i>
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions - <i>lines 230 – 239, 249</i>
17			- <i>251</i>
18			
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20	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
21	(masking)		participants, care providers, outcome assessors, data analysts), and
22			how - <i>lines 248 - 260</i>
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25		17b	If blinded, circumstances under which unblinding is permissible, and
26			procedure for revealing a participant's allocated intervention during
27			the trial – <i>lines 261 - 266</i>
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Methods: Data collection, management, and analysis

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31	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
32	methods		trial data, including any related processes to promote data quality (eg,
33			duplicate measurements, training of assessors) and a description of
34			study instruments (eg, questionnaires, laboratory tests) along with
35			their reliability and validity, if known. Reference to where data
36			collection forms can be found, if not in the protocol – <i>lines 332 – 367,</i>
37			<i>Figure 1</i>
38			
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40		18b	Plans to promote participant retention and complete follow-up,
41			including list of any outcome data to be collected for participants who
42			discontinue or deviate from intervention protocols – <i>N/A – pilot study</i>
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45	Data	19	Plans for data entry, coding, security, and storage, including any
46	management		related processes to promote data quality (eg, double data entry;
47			range checks for data values). Reference to where details of data
48			management procedures can be found, if not in the protocol – <i>lines</i>
49			<i>333 – 335, 359 - 367</i>
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52	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
53	methods		Reference to where other details of the statistical analysis plan can be
54			found, if not in the protocol – <i>lines 369 - 382</i>
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56		20b	Methods for any additional analyses (eg, subgroup and adjusted
57			analyses) – <i>lines 369 - 382</i>
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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) – *lines 383 - 387*

Methods: Monitoring

- 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 – *lines 393 - 399*
- 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 – *N/A– interim analysis is not planned*
- 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 – *lines 185 – 195, 346 – 350*
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – *lines 393 - 399*

Ethics and dissemination

- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – *lines 408 – 410*
- 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) – *N/A – pilot study*
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – *lines 413 - 431*
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – *N/A*
- 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 – *lines 359 – 367*
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site – *lines 499 – 500, 508 – 510*
- 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 – *lines 359 – 364*

1			
2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation – <i>N/A</i>
4			
5	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions –
9			<i>lines 512 – 514</i>
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11		31b	Authorship eligibility guidelines and any intended use of professional
12			writers – <i>lines 484 – 489</i>
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14		31c	Plans, if any, for granting public access to the full protocol, participant-
15			level dataset, and statistical code – <i>lines 361 – 361</i>
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19	Appendices		
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21	Informed consent	32	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates – <i>N/A – consent only in Czech</i>
23			<i>language</i>
24			
25	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
26	specimens		specimens for genetic or molecular analysis in the current trial and for
27			future use in ancillary studies, if applicable – <i>N/A</i>
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Effect of Prophylactic Fibrinogen Concentrate In Scoliosis Surgery (EFISS): a study protocol of two-arm, randomised trial

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Complete List of Authors:	Vrbica, Kamil; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine Hudec, Jan; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine Hrdy, Ondrej; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine Galko, Michal; University Hospital Brno, Department of Orthopaedic Surgery; Masaryk University Faculty of Medicine, Department of Orthopaedic Surgery Horalkova, Hana; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine Demlova, Regina; Masaryk University Faculty of Medicine, Department of Pharmacology/CZECRIN Kubelova, Michaela; Masaryk University Faculty of Medicine, Department of Pharmacology/CZECRIN Repko, Martin; University Hospital Brno, Department of Orthopaedic Surgery; Masaryk University Faculty of Medicine, Department of Orthopaedic Surgery Gal, Roman; University Hospital Brno, Department of Anaesthesiology and Intensive Care Medicine; Masaryk University Faculty of Medicine, Department of Anaesthesiology and Intensive Care Medicine
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1 **Effect of Prophylactic Fibrinogen Concentrate In Scoliosis** 2 **Surgery (EFISS): a study protocol of two-arm, randomised trial**

3
4 Vrbica K¹, Hudec J¹, Hrdy O¹, Galko M³, Horalkova H¹, Demlova R⁴, Kubelova M⁴,
5 Repko M³, Gal R¹

- 6
7 1) Department of Anaesthesiology and Intensive Care Medicine, University
8 Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czech
9 Republic
10 2) Department of Orthopaedic Surgery, University Hospital Brno and Faculty of
11 Medicine, Masaryk University, Brno, Czech Republic
12 3) Department of Pharmacology/CZECRIN, Faculty of Medicine, Masaryk
13 University, Brno, Czech Republic

14 **Correspondence to:** Jan Hudec, hudeja@gmail.com, University Hospital Brno and
15 Faculty of Medicine, Masaryk University, Brno, Jihlavská 20, 625 00 Brno, Czech
16 Republic

17 **Word count:** 3828 words

39 Abstract

41 Introduction

42 Fibrinogen is one of the essential coagulation factors. Preoperative lower
43 plasma fibrinogen level has been associated with higher blood loss. Scoliosis
44 surgery presents a challenge for the anaesthetic team, one of the reasons being
45 blood loss and transfusion management. Recently, the prophylactic fibrinogen
46 administration has been a debated topic in various indications. It has been described
47 e.g. in urological or cardiovascular surgery, as well as in paediatrics. This pilot study
48 is focused on verifying the feasibility of potential large randomised trial and verifying
49 the safety of prophylactic fibrinogen administration in paediatric scoliosis surgery.

50 Methods and analysis

51 A total of 32 paediatric patients indicated for scoliosis surgery will be
52 recruited. Participants will be randomised into study groups in a 1:1 allocation ratio.
53 Patients in the intervention group will receive prophylactic single dose of fibrinogen,
54 in addition to standard of care. Patients in the control group will receive standard of
55 care without study medication prior to skin incision. The primary aim is to assess the
56 safety of prophylactic fibrinogen administration during scoliosis surgery in children,
57 the incidence of any adverse events (AEs) and reactions will be monitored during
58 participation in the study. The secondary objective is to investigate the additional
59 safety information, feasibility and efficacy of a prophylactic fibrinogen administration.
60 The incidence of AEs and reactions according to selected Adverse Events of Special
61 Interest will be monitored. All collected data will be subjected to statistical analysis
62 according to a separate Statistical Analysis Plan.

63 Ethics and dissemination

64 This trial follows the applicable legislation and requirements for good clinical
65 practice according to the ICH E6(R2). All essential trial documents were approved by
66 the relevant ethics committee and national regulatory authority (State Institute for
67 Drug Control) and their potential amendments will be submitted for approval.

68 Trial registration number and protocol version

69 ClinicalTrials.gov Identifier: NCT05391412
70 EudraCT No.: 2021-005493-25. Protocol version is 1.1 of the date 28/2/2022.

73 Key words

74 scoliosis, fibrinogen, paediatrics, orthopaedic, anaesthesiology

76 Strength and limitations of the study

- 77 1. Results of this study might improve knowledge about prophylactic fibrinogen
78 administration in the paediatric population during scoliosis surgery.
- 79 2. The results of this feasibility study will provide data to plan a fully powered
80 randomised trial.

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3 81 3. Results of this study might support the claim about the safety of the fibrinogen
4 82 administration before surgery.
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7 84 4. The participants are younger than 18 years at the time of recruitment,
8 85 according to national legislation, the informed consent must be signed by both
9 86 parents or legal guardians.

10 87 5. The feasibility assessment may indicate a lack of data to determine the
11 88 influence on blood loss and bleeding management.
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For peer review only

124 Background

125 Scoliosis is defined as an abnormal lateral deviation of the spine of more than
126 10° in the frontal plane, with deviation in the sagittal plane and vertebral rotation. It is
127 one of the most common spinal deformities in children (1–3). The approach to the
128 treatment is multidisciplinary and depends on the scoliotic curve severity and
129 progression (4). The surgery is commonly indicated in patients with progressive
130 curves and Cobb angle over 40° to stop further progression of the curve and prevent
131 the development of multiple organ disease (5). Except for musculoskeletal disorders,
132 cardiovascular, respiratory, gastrointestinal, or psychosocial problems are described
133 in patients with scoliosis (6). Anaesthesia for scoliosis surgery is a highly challenging
134 task for the whole team. The specifics of such anaesthesia include e.g. long
135 operation time, body temperature decrease, high blood losses, positioning, or
136 intraoperative neurophysiological monitoring (7,8).

137 During scoliosis surgery, high blood loss and the necessity of blood
138 transfusions are described, while allogeneic derivatives are necessary in the
139 perioperative period in about 30 % to 60 % of cases (9). Bleeding complications and
140 adverse events associated with blood transfusions prolong and increase the cost of
141 hospitalisation and increase the mortality (10). Well-known and commonly applied
142 approaches to reduce blood loss include antifibrinolytics, such as tranexamic acid,
143 which can be administered before surgery (11,12), permissive hypotension, which
144 can be used to reduce blood loss. Prevention of hypothermia is another way to
145 reduce bleeding, and cell salvage, especially in high-risk patients, where it is
146 preferred to minimise allogeneic blood transfusions (13).

147 Fibrinogen is essential for clot formation and stopping bleeding (14,15).
148 Hypofibrinogenemia or dysfibrinogenemia leads to more severe bleeding during
149 high-extensive surgery (16–18). Moreover, some studies describe less blood loss in
150 patients with higher preoperative fibrinogen levels (19). Prophylactic administration
151 of fibrinogen is a widely discussed theme, but to date, the data are limited (20).
152 Some studies described a significant reduction in blood loss and a secondary
153 reduction in allogeneic derivatives administration. Prophylactic fibrinogen
154 administration has been described in cardiovascular or urological surgery (21–23).
155 Additionally, early administration has been reported to be safe in the paediatric
156 population (24).

157 However, the effect of prophylactic fibrinogen administration in paediatric
158 scoliosis surgery remains unclear. We designed this study to verify the feasibility of
159 prophylactic fibrinogen administration in paediatric scoliosis surgery. The results will
160 be used to plan a sufficiently large randomised trial with the aim to clarify the impact
161 of prophylactic fibrinogen application on the magnitude of blood loss and the need
162 for transfusion. This study is focused on the safety, efficacy, and feasibility of
163 prophylactic administration of fibrinogen in scoliosis surgery. The clinical outcome of
164 each participant is studied, particularly the incidence of potential adverse events
165 such as thromboembolism, allergic reactions, or fevers. The results of this study may

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3 166 improve knowledge about prophylactic fibrinogen application. All participants in this
4 167 study will contribute to this socially beneficial knowledge.
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8 169 **Methods and analysis**

9 170 10 171 **Study design**

11 172 The setting of the study is two-arm, prospective, monocentric, randomised,
12 173 double-blind pilot trial with a 1:1 allocation ratio testing safety, efficacy and feasibility
13 174 of prophylactic fibrinogen administration during scoliosis surgery in the paediatric
14 175 population. The pilot study started on 1/6/2022 and the estimated end of the study is
15 176 planned on 30/9/2023. The study protocol is compiled according to the SPIRIT
16 177 (Standard Protocol Items: Recommendations for Interventional Trials) checklist (25).
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19 179 **Aims and objectives**

20 180 This pilot study is conducted before designing a fully powered study. This pilot
21 181 study aims to assess the safety, feasibility, and efficacy of prophylactic fibrinogen
22 182 administration during scoliosis surgery in the paediatric population. Results from this
23 183 pilot study will be used to optimise the fully powered study design and determine the
24 184 final sample size.

25 185 The primary aim of a pilot study is to assess the safety of perioperative
26 186 infusion of fibrinogen during scoliosis surgery in children. The incidence of any
27 187 adverse events (AEs), adverse drug reactions, serious adverse events, serious
28 188 adverse reactions, unexpected adverse reactions and suspected unexpected serious
29 189 adverse reactions will be monitored during participation in the study. These primary
30 190 outcomes monitoring respects European directive 2001/20/EC (26).
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33 192 The secondary aim is to investigate the additional safety information,
34 193 feasibility and efficacy of a prophylactic administration of fibrinogen. The incidence of
35 194 adverse events and reactions according to the following Adverse Events of Special
36 195 Interest (AESI) will be monitored. Monitored AESI include deep vein thrombosis
37 196 verified on ultrasound imaging, pulmonary embolism confirmed on CT scan and
38 197 infection or healing disorder requiring re-surgery and/or the initiation of antibiotic
39 198 therapy. Additional safety information include ICU and hospital length of stay (days)
40 199 and 28-day mortality.

41 200 Other endpoints and monitored parameters, such as additional safety
42 201 information, demographic characteristics, laboratory values, comparison of blood
43 202 loss, or feasibility assessment, are mentioned in the section "Data collection."
44
45 203

46 204 **Participants**

47 205 *Eligibility criteria*

48 206 All patients admitted to the hospital for scoliosis surgery will be screened for
49 207 inclusion criteria. When inclusion criteria will be met, the exclusion criteria will be
50 208 checked. Only patients with fulfilled all inclusion criteria and without all exclusion
51 209 criteria will be considered for participation in the study.

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3 2094 210 *Inclusion criteria are as follows:*

- 6 211 • Elective scoliosis surgery.
- 7 212 • Age < 18 years at the time of enrollment.
- 8 213 • Signed the relevant informed consent form.
- 10 214 • Sexually active participants (≥ 15 years old) must agree to the use of following
11 215 methods of contraception for the duration of this clinical trial:
 - 12 216 • Women - proper use of a highly reliable method of contraception, i.e.
14 217 combined hormonal contraception (oral, vaginal or transdermal form),
15 218 gestagen hormonal contraceptives associated with ovulation inhibition
16 219 (oral or injectable form) or sexual abstinence.
 - 18 220 • Men - sexual abstinence or the use of an adequate contraceptive
19 221 method (i.e. condom) in case of sexual intercourse.

20 222 *Exclusion criteria are as follows:*

- 22 223 • Diagnosed congenital or acquired coagulopathy.
- 23 224 • Use of anticoagulants with the exception of perioperative prophylactic
24 225 administration of low-molecular-weight-heparin (LMWH) to prevent venous
25 226 thromboembolism (VTE).
- 27 227 • Known hypersensitivity to the active substance or to any of the excipients of
28 228 Investigational Medicinal Product (IMP).
- 29 229 • History of deep vein thrombosis or pulmonary embolism.
- 31 230 • Pregnancy and lactation.

32 231

33 232 **Recruitment and withdrawal**

35 233 The study is conducted at University Hospital Brno, Czech Republic, in
36 234 cooperation with the Department of Anaesthesiology and Intensive Care Medicine
37 235 and the Department of Orthopaedic Surgery. The study is controlled by research
38 236 infrastructure CZECRIN. All patients eligible for the study and the patient's parents/
39 237 legal guardians will be asked to participate in the EFISS study. The informed consent
40 238 has to be signed by both parents or legal guardians. For patients who reach the age
41 239 of 12 at the time of enrollment, adapted written information and an informed consent
42 240 is prepared considering the level of knowledge and the age of patients. All
43 241 participants or their parents / legal guardians can withdraw at any time without giving
44 242 any reason, but they must notify the investigator.

45 243

46 244 **Sample size**

48 245 Since this is a pilot study, a power calculation to determine sample size is not
49 246 required. The sample size was defined in consensus by the State Institute of Drug
50 247 Control of the Czech Republic, statisticians and investigators. Thirty participants (15
51 248 in both arms) were defined as a sample size according to standard guidelines for
52 249 pilot studies and recommendation of good practice (27–29). Considering a 5%
53 250 dropout rate, 32 participants will be recruited.

54 251

55 252 **Randomisation and blinding**

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2
3 253 Patients will be randomised in a 1:1 ratio to receive fibrinogen or standard of
4 254 care without further study medication. Randomisation will be performed electronically
5 255 in the electronic case report form (eCRF) REDCap database. This eCRF was
6 256 created by study statisticians and study data managers and contains a
7 257 randomization list. Unblinded person will perform the randomization after controlling
8 258 all inclusions and exclusions criteria before induction to the anaesthesia. Based on
9 259 the randomisation process, an unblinded person indicates IMP application / non-
10 260 application before skin incision.

11 261 The study medication will be prepared by the unblinded study nurse outside
12 262 the operating theatre. It will be administered after induction of anaesthesia before the
13 263 beginning of surgery under the supervision of an unblinded investigator. The study
14 264 nurse and investigator will be unblinded for the duration of this study and will not be
15 265 part of the operating team. The blinded surgical team (orthopaedist,
16 266 anaesthesiologist, and anaesthesiology nurse) will be outside the theatre during the
17 267 IMP application / non-application. The unblinded study team maintains the
18 268 anaesthesia respecting local protocol for paediatric scoliosis anaesthesia during the
19 269 IMP application / non-application. After IMP application/ non-application, unblinded
20 270 study nurse and unblinded investigator will leave the operating room, and the blinded
21 271 operating team will enter back to the theatre. Based on these blinding measures, we
22 272 are able to ensure absolute blinding of the surgical team.

23 273 The data management group and statisticians will work with a pseudo-
24 274 anonymised data set. Emergency unblinding before the end of the study should
25 275 occur only in exceptional circumstances when knowledge of the actual treatment is
26 276 necessary for further management of the patient's treatment. This activity can be
27 277 performed directly in the REDCap electronic database. The investigator must report
28 278 all unblindings (with reason) as they occur on the corresponding eCRF page.
29 279

30 280 **Intervention**

31 281 *Choice of comparators*

32 282 Bleeding and coagulopathy are present during scoliosis surgery, and lack of
33 283 fibrinogen plays a crucial role in it. We decided to reduce blood loss and
34 284 coagulopathy development, the fibrinogen will be administered preventively in the
35 285 intervention arm. The standard of care presents respecting local protocol based on
36 286 international guidelines (see below). This standard approach will be compared with
37 287 the intervention.

38 288 *Standard of care*

39 289 All study participants will receive standard of care in blood and coagulation
40 290 management for scoliosis surgery. Blood tests including haemoglobin (Hb),
41 291 hematocrit (Htc), platelet count (Plt), fibrinogen level (Fbg), activated partial thrombin
42 292 time (aPTT), prothrombin time (PT), and thrombin time (TT) will be performed before
43 293 the surgery. Values will be checked before surgery, and in case of significant
44 294 pathology, the surgery will be delayed and the haematologist will be invited.
45 295 Tranexamic acid will be administered to all patients before the skin incision in a dose
46 296 of 10-15 mg/kg. The standard of care includes the restrictive administration of blood

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3 297 transfusion, plasma derivative, and fluids during the perioperative period. The
4 298 anesthesiologist or attending physician in the ICU will administer fluids, blood
5 299 transfusions, and derivatives depending on clinical judgement, blood loss, blood
6 300 count, coagulation tests, and vital signs. This administration is directed by the local
7 301 protocol of the investigator's hospital which respects international guidelines. "Goal
8 302 directed therapy" approach is preferred in case of bleeding in perioperative period.
9 303 When the blood loss exceeds about 25% of estimated total blood volume of the
10 304 patient, blood samples (blood count, coagulation status and/or viscoelastic
11 305 haemostatic assay) are performed and blood transfusions and derivatives are
12 306 managed according to the results. The goals during bleeding are haemoglobin 7-9
13 307 g/dL, fibrinogen above 2 g/L, platelets above $50 \times 10^9/L$ and normalisation of
14 308 coagulation status. In case of life-threatening bleeding, the transfusion strategy of
15 309 fibrinogen concentrate with red blood cells or fresh frozen plasma with red blood
16 310 cells in ratio of at least 1:2 is performed. The local protocol respects international
17 311 guidelines (30).

312 *Intervention description*

313 Participants in the intervention group will receive the standard of care, and in
314 addition, a single dose of fibrinogen prior to the skin incision. IMP is administered
315 intravenously and is immediately available at a plasma concentration corresponding
316 to the dose. It is in a powder form in a vial, and it is necessary to solve this powder
317 carefully. The reconstitution procedure should follow the instructions in the package
318 leaflet. Patients in the intervention group will receive a single dose of IMP
319 intravenously, 20–30 mg/kg. This dose range is based on the package leaflet and
320 investigators will administer IMP in doses of hundreds of mg in this range (rounded
321 to closest hundred in dose range). The medicinal product will be diluted in a 100 ml
322 infusion bag and will be administered after induction to anaesthesia before surgery.
323 The infusion rate should not exceed approximately 5 ml per minute. The IMP will be
324 administered according to the above study blinding rules.

325

326 **Comparison**

327 Participants in the intervention group will receive standard of care and IMP
328 before skin incision. Participants in the control group will receive standard of care
329 without study medication before skin incision. In the control group the placebo will
330 not be administered. It is caused by the requirements of the national regulatory
331 authority (State Institute of Drug Control of the Czech Republic), which does not
332 allow the administration of a placebo in the paediatric population unless it has
333 therapeutic or preventive effect.

334 The blinded operating team will manage both groups according to the
335 standard of care after the initial intervention/non-intervention. Therefore, fibrinogen
336 can be administered to all patients if indicated in perioperative period according to
337 the local protocol for bleeding management (see above).

338 Primary and secondary outcomes will be compared between intervention and
339 control groups to assess the potential feasibility of a large-scale study.

340

341 **Trial feasibility**

342 The trial feasibility assessment is one of the secondary aims of this study. We
343 will monitor the recruitment rate of eligible patients who will be approached for
344 consent to participate. The feasibility criterion is more than 75 % of enrolled
345 participants. We will also evaluate the percentage of missing outcomes and clinical
346 data. The goal is to have less than 10 % missing outcome data, including ICU and
347 hospital length of stay (LOS) and survival, and less than 10% missing clinical data
348 obtained from clinical medical notes and electronic patient records.

350 **Clinical outcomes**

351 The clinical outcome focuses on reducing blood loss and transfusions in
352 paediatric patients after prophylactic fibrinogen administration during scoliosis
353 surgery. Blood loss and plasma derivatives management will be reported for each
354 participant. Blood count and coagulation parameters will be monitored before
355 surgery, in the end, and 24 hours after the surgery. All parameters will be recorded in
356 the eCRF database.

358 **Data collection**

359 During the course of the trial, subjects will be monitored during hospitalisation
360 and after discharge. According to medical records, all data will be collected in an
361 eCRF. Data of blood count (Hb, Hct, Plt) and coagulation status (PT, aPTT, TT, Fbg)
362 will be filled in eCRF before surgery, after surgery, and 24 hours after surgery.
363 Information about inclusion and exclusion criteria, informed consent, and
364 demographic data will be obtained on the day of enrollment. Collected participant
365 demographic data will be age (years), sex (male, female), weight (kilograms) and
366 Cobb's angle (°). Blood samples will be taken before surgery according to standard
367 of care, post-operative blood samples will be taken immediately after surgery and 24
368 h after surgery. We will record operative time, blood loss, the volume of blood loss
369 for the surgical segment of the spine, and urinary output during surgery and 24 hours
370 after surgery. We will track the number, type, and volume of administered transfusion
371 products, plasma derivatives, crystalloid solutions, and colloid solutions during
372 surgery and in 24 hours postoperative period. The critical part of monitored data will
373 be the incidence of adverse events and reactions according to the following AESI.
374 These reactions will include deep-vein thrombosis verified on ultrasound imaging,
375 pulmonary embolism confirmed on CT, infection or healing disorder requiring re-
376 surgery, and/or the initiation of antibiotic therapy. Ultrasound imaging or CT scan will
377 be indicated individually, only in patients with suspicion of AESI according to the
378 clinical condition.

379
380 Other monitored additional safety information will be:

- 381 • Hospital LOS.
- 382 • Intensive care length of stay (ICU LOS) (day of admission and day of
383 discharge will be counted as one day).

- 384 • 28-day mortality (number of patients who are not alive 28 days after
385 randomization).

386 According to the SPIRIT checklist the schedule of enrollment, interventions, and
387 assessments is summarised in Table 1 (25).

388

389 **Table 1:** Clinical trial schedule

TIMEPOINT	STUDY PERIOD						
	Screening	Allocation	Post-allocation		Hospital discharge	Follow-up	Premature termination
	D_0	D_{0-1}	D_1	D_2	D_{3-28}	D_{28}	Anytime
ENROLMENT:							
Inclusion/Exclusion criteria	X						
Informed consent	X						
Pregnancy testing ¹	X						
Randomization		X					
INTERVENTION:							
Study medication application ²			X				
ASSESSMENTS:							
Demographic data ³	X						
Adverse events			X	X	X	X	X
Laboratory testing ⁴			X	X			
Blood loss ⁵			X	X			
Urinary output ⁶			X	X			
Transfusion products consumption ⁷			X	X			
Fluid therapy ⁷			X	X			
ICU LOS (days)					X		
LOS (days)					X		
28-day mortality						X	
Reason for premature termination							X

390

391 1 urine pregnancy testing

392 2 fibrinogen infusion or standard of care

393 3 age, sex, weight, Cobb's angle

394 4 haemoglobin, haematocrit, platelet count, fibrinogen, aPTT, PT, TT

395 5 volume (ml) during surgery and in the 24-hour postoperative period and volume (ml) related to the surgical segment of the spine

396 6 volume (ml) in the 24-hour postoperative period

397 7 type and volume (ml) during surgery and in the 24-hour postoperative period

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All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and other listings that link participant ID numbers to additional identifying information will be stored in a locked file in an area with limited access. No later than 3 years after the collection of the 1-year post-randomization, we will deliver a completely blinded data set to an

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2
3 408 appropriate data repository for sharing purposes. Statistical codes will be archived in
4 409 accordance with SOPs.

5 410

7 411 **Statistical analysis**

8 412 A separate Statistical Analysis Plan (SAP) will be prepared to provide details
9 413 on the approach to analyses. The SAP will be finalised before the database lock. All
10 414 eventual deviations from the SAP will be described and justified in the relevant part
11 415 of the Clinical Trial Report. As a general approach for the descriptive analysis, the
12 416 following statistics will be provided for continuous variables: the number of subjects
13 417 with available data (n), mean, standard deviation, median, minimum and maximum.
14 418 The number and percentage of patients will be provided for categorical variables. For
15 419 a comparison of continuous variables between treatment groups two-sample t-test or
16 420 its nonparametric alternative Mann-Whitney test will be used, where appropriate.
17 421 Pearson's chi-square test or Fisher exact test will be used to compare categorical
18 422 variables, where appropriate. All statistical tests will be two-sided. P-values < 0.05
19 423 will constitute statistically significant differences. During the pilot study the interim
20 424 analysis is not planned.

21 425 Protocol non-adherence will be assessed by the principal investigator case by
22 426 case. Patients with major deviations from the study protocol will be excluded from
23 427 the analysis. Missing data are not planned to be imputed. However, in the event of
24 428 substantial missing data for any parameter, a sensitivity analysis using any method
25 429 of imputation could also be used.

26 430 **Patient and public involvement**

27 431 Patients or the public will not be involved in the study development. This
28 432 EFISS study was proposed and designed by an expert team of University Hospital
29 433 Brno and the Faculty of Medicine, Masaryk University Brno in the Czech Republic.
30 434

31 435 **Monitoring and auditing**

32 436 The trial centre will be monitored according to the monitoring plan provided by
33 437 research infrastructure CZECRIN. The objectives of the monitoring are to ensure that
34 438 the trial participant's safety and rights are respected, that accurate, valid and
35 439 complete data are collected, and that the trial is conducted in accordance with the
36 440 trial protocol, the principles of GCP and national legislation. Sponsor, Regulatory
37 441 authority and Ethics committees have the right to inspect/audit the trial site.
38 442

39 443 **Ethics and dissemination**

40 444 This trial follows the applicable legislation and requirements for good clinical
41 445 practice according to the ICH E6(R2). Compliance with this standard provides public
42 446 assurance that the rights, safety, and well-being of trial participants are protected
43 447 and that the clinical trial data are credible.

44 448 All essential trial documents were approved by the relevant ethics committee
45 449 and national regulatory authority (State Institute for Drug Control) and their potential
46 450 amendments will be submitted for approval. The study was approved by University
47 451 hospital Brno's Ethics Committee (No.: 24/22MONO) and by State Institute for Drug

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3 452 Control (No.: sukls11048/2022). This clinical study includes patients belonging to the
4 453 category of vulnerable subjects, namely children and adolescents under 18 years of
5 454 age.

7 455 *Informed consent procedure*

8 456 The parents / legal guardians will receive written information and an informed
9 457 consent form (ICF). The investigator will inform in a comprehensible manner about
10 458 the nature, purpose, and significance of the clinical trial simultaneously. This
11 459 procedure will take place before enrolling the child in the study. Parents / legal
12 460 guardians will also be informed of the measures to protect personal data. That
13 461 liability insurance has been arranged for investigators and sponsors in the event of
14 462 health damage due to a clinical trial, including possible compensation for trial
15 463 subjects. Paediatric patients will receive from the investigator information on the
16 464 clinical trial adapted to their level of knowledge and intellectual abilities, including
17 465 details on the benefits and risks of participating in this clinical trial. The explicit wish
18 466 of instructed paediatric patients to refuse to participate or to withdraw from a clinical
19 467 trial at any time is always respected. Written information and an informed assent
20 468 form are prepared for patients who reach the age of 12 at the time of enrollment.
21 469 Paediatric patients and their parents / legal guardians will get sufficient time to study
22 470 the written information and the informed consent form carefully and will ask
23 471 additional questions to which the investigator must respond satisfactorily. All legal
24 472 representatives (both parents) will must sign the informed consent form at the end of
25 473 the process.

32 474 *Supervision of the informed consent procedure*

33 475 The process of obtaining informed consent from the patient's parents / legal
34 476 guardians, or patients, must always be adequately documented by the investigator
35 477 using valid forms and the patient's medical records. The clinical trial monitor will
36 478 check the process during monitoring visits. Significant deviations in the process will
37 479 lead to the termination of the patient's participation in the trial.
40 480

41 481 **Discussion**

42 482 Prophylactic fibrinogen administration before high-risk surgeries is a widely
43 483 discussed topic across medical fields. Preoperative lower levels of fibrinogen are
44 484 associated with higher blood loss in adolescent idiopathic scoliosis surgery.
45 485 However, if the effect of prophylactic fibrinogen administration will lead to blood loss
46 486 reduction in these patients is unclear (17,18,31).

47 487 The safety of fibrinogen administration in the paediatric population has been
48 488 demonstrated in several studies (24,32). However, in these studies, fibrinogen was
49 489 substituted during the surgery according to the viscoelastic haemostatic assays, the
50 490 substitution was not prophylactic. In addition, the number of participants was low. In
51 491 summary, data on prophylactic administration in children and adolescents are
52 492 insufficient, more studies are needed.

53 493 We can see some similarity with tranexamic acid administration. In recent
54 494 years, tranexamic acid has been commonly used in scoliosis surgery to reduce blood
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3 495 loss (33–35). The efficacy of tranexamic acid is unambiguous, it reduces blood loss,
4 496 the need for blood transfusions and the length of hospitalisation (33). The use of
5 497 tranexamic acid is incorporated in orthopaedic recommendations for blood
6 498 management (36). However, some studies have provided evidence of the
7 499 thromboembolic potential of tranexamic acid (37,38). In contrast, fibrinogen is not
8 500 associated with higher thromboembolic risk repeatedly (39). It is appropriate to study
9 501 fibrinogen concentrate to see if it has the same positive properties as tranexamic
10 502 acid without possible side effects.

11 503 This pilot study also has some limitations. The sample size is designed
12 504 according to standard guidelines for pilot studies, so it is limited to 32 patients.
13 505 Participants are under the age of 18, so informed consent has to be signed by both
14 506 parents or legal guardians, which may lead to limited enrollment. Data are collected
15 507 28 days after randomisation, which may not be an adequate interval to evaluate
16 508 safety and feasibility. And final limitation is the absence of placebo administration in
17 509 the standard of care group. This absence is mainly caused by the requirements of
18 510 the national regulatory authority, which does not allow the administration of a
19 511 placebo without a therapeutic or preventive effect in the paediatric population.
20 512

21 513 **Conclusion**

22 514 This pilot study should demonstrate the safety and feasibility of the intended
23 515 intervention and form the basis for a later large study which could have extensive
24 516 impact in scoliosis surgery and bleeding management. But the results will not prove
25 517 most likely the efficacy of prophylactic administration of fibrinogen in scoliosis
26 518 surgery.
27 519

28 520 **Acknowledgements**

29 521 The authors thank everyone involved in the study, concretely the participants,
30 522 assessors and all health care providers taking care for participants.
31 523

32 524 **Contributions**

33 525 OH, RG first conceived this protocol after revision from the other authors. KV,
34 526 JH, MG are the main authors and editors of this manuscript. MG, MR are responsible
35 527 for patient involvement. JH, KV, HH provide standards of care. CZECRIN (MK, RD)
36 528 assisted in the development of the study protocol and is responsible for statistical
37 529 analysis. All authors read and approved the final version of the manuscript.
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40 532

41 533 **Sponsor**

42 534 Name and contact information for the trial sponsor:

43 535 Trial Sponsor: Masaryk University Brno

44 536 Contact name: prof. Martin Smrcka, MD, PhD, MBA
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46 538
47 539
48 540

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3 537 Address: Jihlavská 20, 625 00 Brno

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5 538 Telephone: +420532232884

6 539 Email: smrcka.martin@fnbrno.cz

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9
10 541 The sponsor has no role in the design of this trial and will not have any role during its
11 542 execution, analyses, interpretation of the data, or the decision to submit results.

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14 543

15 544 **Funding**

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18 547 development of research organisation (FNBr, 65269705). The project was supported
19 548 by the national budget through MEYS, RI CZECRIN (LM2018128).

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21 549

22 550 **Conflict of interest**

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24
25 551 In the past 5 years, KV and RG have received honoraria for lecturing from
26 552 CSL Behring.

27 553

28 554 **Plan**

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30 555 We intend to submit the results of the study to be published in a peer-reviewed
31 556 international medical journal. The author team will not change.

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STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym – <i>lines 1-2</i>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry – <i>lines 68-70</i>
	2b	All items from the World Health Organization Trial Registration Data Set - <i>lines 68-69</i>
Protocol version	3	Date and version identifier – <i>line 70</i>
Funding	4	Sources and types of financial, material, and other support <i>lines 500 - 504</i>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors – <i>lines 4 – 13 and 482 - 487</i>
	5b	Name and contact information for the trial sponsor – <i>lines 489 - 495</i>
	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 - <i>lines 497 - 498</i>
	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) <i>lines 392 - 398</i>
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 - <i>lines 137 - 167</i>
	6b	Explanation for choice of comparators - <i>lines 305 – 313</i>
Objectives	7	Specific objectives or hypotheses - <i>lines 179 - 198</i>

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2 Trial design 8 Description of trial design including type of trial (eg, parallel group,
3 crossover, factorial, single group), allocation ratio, and framework (eg,
4 superiority, equivalence, noninferiority, exploratory) - *lines 171 - 177*
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8 **Methods: Participants, interventions, and outcomes**
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10 Study setting 9 Description of study settings (eg, community clinic, academic hospital)
11 and list of countries where data will be collected. Reference to where
12 list of study sites can be obtained – *lines 172 - 173, 492 - 496*
13

14 Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility
15 criteria for study centres and individuals who will perform the
16 interventions (eg, surgeons, psychotherapists) - *lines 200 - 227*
17
18

19 Interventions 11a Interventions for each group with sufficient detail to allow replication,
20 including how and when they will be administered – *lines 268 - 303*
21
22 11b Criteria for discontinuing or modifying allocated interventions for a
23 given trial participant (eg, drug dose change in response to harms,
24 participant request, or improving/worsening disease) – *line 186 – 195,*
25 *237 – 239, 383 – 387*
26
27

28 11c Strategies to improve adherence to intervention protocols, and any
29 procedures for monitoring adherence (eg, drug tablet return,
30 laboratory tests) – *N/A*
31

32 11d Relevant concomitant care and interventions that are permitted or
33 prohibited during the trial – *lines 276 - 291*
34

35 Outcomes 12 Primary, secondary, and other outcomes, including the specific
36 measurement variable (eg, systolic blood pressure), analysis metric
37 (eg, change from baseline, final value, time to event), method of
38 aggregation (eg, median, proportion), and time point for each
39 outcome. Explanation of the clinical relevance of chosen efficacy and
40 harm outcomes is strongly recommended - *lines 179 – 198, 324 - 367*
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43 Participant 13 Time schedule of enrolment, interventions (including any run-ins and
44 timeline washouts), assessments, and visits for participants. A schematic
45 diagram is highly recommended (see Figure) – *Figure 1.*
46
47

48 Sample size 14 Estimated number of participants needed to achieve study objectives
49 and how it was determined, including clinical and statistical
50 assumptions supporting any sample size calculations – *lines 241 -*
51 *245*
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54 Recruitment 15 Strategies for achieving adequate participant enrolment to reach
55 target sample size – *229 – 234*
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57 **Methods: Assignment of interventions (for controlled trials)**
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59 Allocation:
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2	Sequence	16a	Method of generating the allocation sequence (eg, computer-
3	generation		generated random numbers), and list of any factors for stratification.
4			To reduce predictability of a random sequence, details of any planned
5			restriction (eg, blocking) should be provided in a separate document
6			that is unavailable to those who enrol participants or assign
7			interventions – <i>lines 247 - 251</i>
8			
9			
10	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
11	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
12	mechanism		describing any steps to conceal the sequence until interventions are
13			assigned – <i>lines 249 - 251</i>
14			
15	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
16			and who will assign participants to interventions - <i>lines 230 – 239, 249</i>
17			- <i>251</i>
18			
19			
20	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
21	(masking)		participants, care providers, outcome assessors, data analysts), and
22			how - <i>lines 248 - 260</i>
23			
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25		17b	If blinded, circumstances under which unblinding is permissible, and
26			procedure for revealing a participant's allocated intervention during
27			the trial – <i>lines 261 - 266</i>
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Methods: Data collection, management, and analysis

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30			
31	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
32	methods		trial data, including any related processes to promote data quality (eg,
33			duplicate measurements, training of assessors) and a description of
34			study instruments (eg, questionnaires, laboratory tests) along with
35			their reliability and validity, if known. Reference to where data
36			collection forms can be found, if not in the protocol – <i>lines 332 – 367,</i>
37			<i>Figure 1</i>
38			
39			
40		18b	Plans to promote participant retention and complete follow-up,
41			including list of any outcome data to be collected for participants who
42			discontinue or deviate from intervention protocols – <i>N/A – pilot study</i>
43			
44			
45	Data	19	Plans for data entry, coding, security, and storage, including any
46	management		related processes to promote data quality (eg, double data entry;
47			range checks for data values). Reference to where details of data
48			management procedures can be found, if not in the protocol – <i>lines</i>
49			<i>333 – 335, 359 - 367</i>
50			
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52	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
53	methods		Reference to where other details of the statistical analysis plan can be
54			found, if not in the protocol – <i>lines 369 - 382</i>
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56		20b	Methods for any additional analyses (eg, subgroup and adjusted
57			analyses) – <i>lines 369 - 382</i>
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- 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) – *lines 383 - 387*

Methods: Monitoring

- 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 – *lines 393 - 399*
- 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 – *N/A– interim analysis is not planned*
- 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 – *lines 185 – 195, 346 – 350*
- Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor – *lines 393 - 399*

Ethics and dissemination

- Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval – *lines 408 – 410*
- 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) – *N/A – pilot study*
- Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) – *lines 413 - 431*
- 26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable – *N/A*
- 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 – *lines 359 – 367*
- Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site – *lines 499 – 500, 508 – 510*
- 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 – *lines 359 – 364*

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2	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and for
3	post-trial care		compensation to those who suffer harm from trial participation – <i>N/A</i>
4			
5	Dissemination	31a	Plans for investigators and sponsor to communicate trial results to
6	policy		participants, healthcare professionals, the public, and other relevant
7			groups (eg, via publication, reporting in results databases, or other
8			data sharing arrangements), including any publication restrictions –
9			<i>lines 512 – 514</i>
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11		31b	Authorship eligibility guidelines and any intended use of professional
12			writers – <i>lines 484 – 489</i>
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14		31c	Plans, if any, for granting public access to the full protocol, participant-
15			level dataset, and statistical code – <i>lines 361 – 361</i>
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19	Appendices		
20			
21	Informed consent	32	Model consent form and other related documentation given to
22	materials		participants and authorised surrogates – <i>N/A – consent only in Czech</i>
23			<i>language</i>
24			
25	Biological	33	Plans for collection, laboratory evaluation, and storage of biological
26	specimens		specimens for genetic or molecular analysis in the current trial and for
27			future use in ancillary studies, if applicable – <i>N/A</i>
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