Protocol

Study ID: NN7711-4729

Clinical outcomes of NovoSeven® treatment in severe postpartum haemorrhage – a retrospective single-centre cohort study at the University Hospital of Bern

Redacted protocol
Includes redaction of personal identifiable information only.

Non-interventional (NIS)

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Study information

Title	Clinical outcomes of NovoSeven® treatment in severe postpartum haemorrhage – a retrospective single-centre cohort study at the University Hospital of Bern
Protocol author	[redacted], Novo Nordisk A/S, [redacted]
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Procedure number	
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé 2880 Bagsværd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	The primary objective is to evaluate whether NovoSeven® reduces the requirement for invasive procedures in women with an event of severe postpartum haemorrhage.
Country(-ies) of study	CH

Marketing authorisation holder(s)

Marketing authorisation holder(s) (MAH(s))	Novo Nordisk A/S Novo Allé 2880 Bagsværd Denmark
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2 List of abbreviations

ATC	Anatomical Therapeutic Chemical (Classification System)
DDAVP	Desmopressin containing product
EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
FFP	Fresh frozen plasma
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder
NIS	Non-interventional Study
PACU	Post-anaesthesia care unit
PLT	Platelet
PPH	Postpartum haemorrhage
RBC	Red Blood Cells
rFVIIa	Activated recombinant FVII
SAP	Statistical Analysis Plan
sPPH	Severe PPH
TE	Thromboembolic Event
TF	Tissue factor
TXA	Tranexamic Acid
UTN	Universal Trial Number
vWF	*von Willebrand factor*
WHO	World Health Organization

3 Responsible parties

Bern University Hospital will collect the clinical data relevant and specific for this study. Bern University Hospital will transfer the data in a pseudonymised format to Novo Nordisk where data analysis will take place.

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

4 Amendments and updates

Amendment or update no	***Date***	***Section of the study protocol***	***Amendment or update***	***Reason***
Version ~~1.1~~2.0	*26-AUG_2020*	*4 Milestones*	*Updates of the milestones*	*Study delay*
		6 Rationale and background	*Editorial changes*	
		7.2 Estimand	*Editorial changes together with inclusion of a rational for the estimand*	*Clarify the estimand*
		8.1.1 Endpoints	*Update of the endpoints: The 20 minute window for evaluating invasive procedure (primary endpoint) and hysterectomy (secondary endpoint) has been deleted as the time0 now include the 20 minutes window*	*This update is primarily technical and has been made to ensure balance between NovoSeven® treated patients and controls at the time of matching (time0)*
		8.3 Variables	*Clarification of variables*	*To better reflect the actual data collection*
		8.7.3.1 Analysis of primary endpoint	*Clarification of the primary population*	*Based on input from PPH experts it has became clear that the previously suggested definition of the primary population will result in a too small population for statistical analysis*

Amendment or update no	***Date***	***Section of the study protocol***	***Amendment or update***	***Reason***
		8.7.3.2 Analysis of secondary endpoints	*Clarification that analysis of secondary endpoint (control of bleeding) will also include a comparison of post-time0 levels. Updates to methods and editorial changes*	*To reflect changes to analysis of primary endpoint*
		8.9 Limitations of research methods	*Editorial changes*	
Version 3.0	22-Dec-2020	*7.1 Primary objective*	*Update of primary objective*	*The primary objective stated before that we are looking into the incidence of invasive procedures. However, the primary endpoint is measuring the occurrence of invasive procedures. Thus, the primary objective was updated from incidence to proportion.*
		7.2 Estimand	*Editorial changes due to the update of the primary endpoint. An explanation of the 20 min lag-time have been added. "Discharge from hospital" was deleted from the Table showing intercurrent events, instead considered as missing data issue for women discharged from hospital. This information is added to Section 8.7.1*	*Due to the update of the primary endpoint. The intercurrent event has been identified as a likely event and a clarification on how to handle it has been added.*

Amendment or update no	***Date***	***Section of the study protocol***	***Amendment or update***	***Reason***
			Additional intercurrent event has been added	
		8.1 Study design	*Update to the data collection period: The retrospective data collection period was updated from January 2005-April 2016 to January 2006-April 2016*	*Ethics committee approval for data collection was received only for the period from January 2006-April 2016*
		8.1.1 Endpoints	*Update of the endpoints: The 20 minute window for evaluating invasive procedure (primary endpoint) and hysterectomy (secondary endpoint) has been added. Revision of wording of Time0* *The definition of time0 is updated*	*This update has been made to better reflect the clinical question "What is the effect of NovoSeven® 20 minutes after its administration (onwards) on invasive procedures", this can be done by the new definition of time0.* *The update of time0 was made to avoid immortal time bias from time of exposure to time of matching.*
		8.7.3.2 Analysis of secondary endpoints	*Addition of supportive analyses* *It was also clarified that an exact conditional logistic regression model will be used. The supportive analysis will be done on the matched population.*	*To evaluate the impact of 20 min lag time in the primary endpoint, supportive analyses are included.*

Amendment or update no	***Date***	***Section of the study protocol***	***Amendment or update***	***Reason***
		8.8.1 Critical documents	*Editorial changes: the text referring to 'informed consent' was deleted as the study does not involve informed consent process*	*Editorial change*
		10 Management and reporting of adverse events/adverse reactions	*The text has been updated to reflect that as the study is based on secondary use of data, Individual Case Safety Report will not be performed in the study*	*This update has been made to follow the standard operating procedure (Non-Interventional and epidemiological studies based on external databases and registries-Q110133) requirements for protocols*

5 Milestones

Milestone	**Planned date**
Start of data collection	29-JUN-2020
End of data collection	~~30-SEP-2020~~ 20 -JAN-2021
Data Transfer	~~*30-SEP-2020*~~ *20-JAN-2021*
Final report of study results	~~20-DEC-2020~~ *01-MAY-2021*

6 Rationale and background

Postpartum haemorrhage (PPH) is usual defined as blood loss of more than 500 mL during vaginal delivery and 1000 mL during caesarean delivery [1]. Blood loss occurring during the first 24 h after delivery, is known as primary PPH and if between 24 h to 12 weeks [2] after delivery, it is termed secondary PPH [3]. PPH can result in anaemia, fatigue, depression, anxiety, loss of fertility, and reduced cognitive capabilities [4-6]. Severe post-partum haemorrhage (sPPH) can be defined as continuous blood loss of at least 1500 mL within 24 h after delivery [7]. Complications following sPPH are often critical and can include organ failure, thromboembolic events (TE) and death. Preventing these complications requires interventions that can involve blood product transfusions, invasive surgery including emergency hysterectomy and admission to the intensive care unit (ICU) [8].

Emergency postpartum hysterectomy may be implemented in sPPH and not infrequently when haemorrhage is uncontrollable and life-threatening [9, 10]. Such a serious intervention has profound implications and means that the women cannot get pregnant again.

The global incidence of PPH is estimated to be 6-11% and 1-3% for sPPH with substantial variations across regions [11]. The incidence of sPPH is undoubtedly higher in low-resource countries compared to high-income countries [11]. Maternal deaths due to PPH can be calculated to be 43 deaths per year in Western Europe when using the WHO PPH cause-specific maternal mortality rate (8%) reported for developed countries [12, 13] and there remains a significant unmet need worldwide to optimize the standard of care.

Consequently, it would be valuable to have an early, effective non-invasive treatment for sPPH available that could reduce the need for major invasive procedures and consequently reduce maternal morbidity and mortality as well as conserving the future reproductive potential of child bearing aged women by avoiding hysterectomy [14].

The treatment options for PPH relate to the underlying cause of haemorrhage: uterotonics for atony, surgical repair of lacerations, removal of retained placental tissue, and correction of coagulopathy when required [4]. Primary uterotonics are routinely administered in the management of the third stage of labour in all parturients at vaginal delivery as well as during caesarean section to prophylactically reduce the risk of PH [15]. Secondary uterotonics are subsequently only administered if primary uterotonics fail [16]. Tranexamic acid (TXA) is frequently added as an antifibrinolytic simultaneously with secondary uterotonics when PPH exceeds 500 mL. In addition to the utilisation of a combination of pharmacological, blood product, mechanical or surgically related interventions, clinicians can consider the use of haemostatic agents including rFVIIa [16, 17]. If colloids or crystalloids are utilized to treat hypovolaemia, they should be used judiciously to avoid dilutional coagulopathy. Fibrinogen can be administered, a fibrinogen level of greater than 2g/L should be maintained during ongoing sPPH if possible [16]. Depending on site expertise and the clinical situation (vaginal birth or caesarean section), intrauterine balloon tamponade or uterine compression

sutures or both are appropriate first line surgical interventions at this juncture. In cases where there is still inadequate control of bleeding, second line invasive interventions including radiological uterine artery embolization, uterine/iliac artery ligation or hysterectomy may be implemented [16].

NovoSeven® is not currently approved for use in sPPH. Current guidelines for management of sPPH differ in the suggested timing of NovoSeven® administration. Nevertheless, early treatment with NovoSeven® in sPPH patients following uterotonic failure and prior to any invasive interventions has been suggested to control bleeding and prevent the need for hysterectomy [14, 18, 19]. The present study intends to substantiate these findings and analyse the use of NovoSeven® as an additional haemostatic agent that could improve patient outcomes if incorporated into the treatment of sPPH at an appropriate time.

The mechanism of action of NovoSeven® bypasses early steps of the coagulation cascade to provide direct activation of the coagulation system at the site of injury. Pharmacological doses of NovoSeven® induce haemostasis not only in haemophilia patients, but also in patients with profuse bleeding triggered by extensive surgery or trauma. At pharmacological doses, NovoSeven® binds to tissue factor (TF), exposed as a result of vascular injury. The complex formed between NovoSeven® and TF enzymatically activates FX and FIX. As a result of these initial reactions, prothrombin is converted into thrombin, resulting in a limited amount of thrombin, sufficient to activate co-factors FVIII and FV and platelets at the site of injury, and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Activation of platelets also increases platelet adhesion. Large amounts of thrombin are generated from the propagation phase, which occurs on the surface of the thrombin-activated platelets through complex formation between FIXa-FVIIIa and between FXa-FVa. As a result, a full burst of thrombin is generated on the thrombin-activated platelet surface. Thrombin is also required for the activation of FXIII, necessary for the cross-linking of fibrin monomers that makes the haemostatic plug more resistant to premature lysis. Thus, a full thrombin burst is essential for the formation of a stable fibrin haemostatic plug that is resistant to premature fibrinolysis, providing a reliable and maintained haemostasis [20]. As the haemostatic effect of NovoSeven® is localised to the site of vascular injury, where TF is exposed and platelets are activated, NovoSeven® does not induce systemic activation of coagulation. Furthermore, early administration ensures that platelets, as well as other coagulation factors such as FVIII and fibrinogen necessary for full thrombin burst and fibrin generation, are still available and not depleted after severe haemorrhage conditions.

NovoSeven® has a well-established safety profile from clinical trials and 23 years of post-marketing experience across multiple indications beyond sPPH. However, a relevant potential risk to be considered with the use of NovoSeven® in sPPH is the risk of developing thromboembolic events (TEs). In general, women giving birth have an underlying higher incidence of TEs compared to other women [21]. In the postpartum period, the incidence of TEs is higher in all parturients during the first 3-6 weeks after delivery, and factors such as caesarean-section, PPH or a body mass index of >30 kg/m^2 may also increase the risk of TEs [21]. When compared to non-pregnant women, the

incidence of TEs is significantly higher during the first postpartum week, declining rapidly thereafter [22]. Nevertheless, the risk remains increased for up to 12 weeks after delivery [23]. The incidence of TEs for women with PPH treated with NovoSeven® has been reported to be 2.5-4.8% [19, 24, 25]. The incidence of TEs in women with PPH in general has been reported to range from <1-7.8 % [26-28]. In brief, the background incidence of TEs in women with PPH is increased regardless of the use of NovoSeven®, but NovoSeven® may contribute to an additional risk increase compared with the background risk of women with PPH.

Literature supports that sPPH patients treated with NovoSeven® exhibit successful control of bleeding. The administration of NovoSeven® prior to invasive procedures has been identified to prevent major invasive interventions including hysterectomy [19, 24, 29]. In addition, a meta-analysis of the use of NovoSeven® in 272 including PPH and sPPH patients demonstrated a successful outcome (85.1% bleeding stopped or reduced) and a low incidence of TEs (2.5 %) [25].

Recommendations for the use of NovoSeven® are included in some national guidelines for treatment of sPPH based on professional consensus-and results from registry studies [2, 30]. The guidelines differ in relation to timing, dosage and number of total doses administered. Consequently, Novo Nordisk aims to develop a more comprehensive understanding of the clinical efficacy and safety of NovoSeven® usage in sPPH by performing analyses of multiple available data sources.

Studies based on observational data can provide valuable additional supportive evidence to that available from randomised clinical trials as they may better reflect the patient population in actual real-world clinical practice outside defined study protocols.

In 2018, Colucci et al. published a single-centre study with data collected from medical records at the Department of Obstetrics at the University Hospital, Inselspital, of Bern, Switzerland[7]. The data consisted of 3 cohorts: 2 historical cohorts and 1 study cohort. The first consisted of data from women with an event of sPPH (defined as >1500 mL blood loss within 24 hours of delivery) treated in the period 2005-2007 (follows in-house guideline on low-dose [60 µg/kg] of NovoSeven®), the second in the period 2008-2010 (followed no standard treatment protocol). The study cohort consisted of women with an event of sPPH treated in the period 2010-2012 (followed a standard PPH management protocol). The treatment protocols for each cohort are presented in Appendix A. The present analysis will include data from the above mentioned 3 cohorts and additionally include a new cohort of women with an event of sPPH treated in the period 2013-2016 according to existing guidelines [31]. The data for the new cohort will be collected retrospectively from electronic medical records. Additional information on timing of different interventions will also be collected for the 3 published cohorts. Throughout the protocol the nomenclature of the cohorts will follow that of the Colucci et al published study [7].

7 Research question and objectives

7.1 Primary objective

~~The primary objective is to compare the incidence of invasive procedures in women with an event of sPPH treated with NovoSeven® to the incidence of invasive procedures in women with an event of sPPH but not treated with NovoSeven®.~~

The primary objective is to compare, in a propensity score matched population of women with severe PPH, the occurrence of any invasive procedure after first treatment with NovoSeven® with the occurrence of any invasive procedure without treatment with NovoSeven®.

Invasive procedures are defined as: uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, or hysterectomy.

7.2 Estimand

The estimand addressed the relative effect of NovoSeven® compared to propensity score matched controls on the occurrence of invasive procedures in women with an event of sPPH. The estimand is defined from the following five elements outlined in the ICH E9(R1):

A. The treatment conditions are NovoSeven® vs. propensity scored matched controls not receiving NovoSeven®.

B. The treatment effect will be estimated for women with an event of sPPH defined by the inclusion criteria in the four cohorts exposed to NovoSeven® and their matched controls.

C. The treatment effect is assessed by the occurrence of invasive procedures within *20 minutes to* 24 hours following ~~matching~~ *time0*.

D. Intercurrent events will be handled by a hypothetical strategy *or a treatment policy strategy* (further details in Table 1).

E. The treatment effect will be quantified by the odds ratio.

Table 1 Handling of intercurrent events for the hypothetical estimand

Intercurrent event	Expected frequency of events	Data collection and analysis
Death	Rare	Death within *the time window for the primary endpoint will be counted as having an invasive procedure* ~~24 hours following matching without a registered invasive procedure will be~~

		~~counted as having an invasive procedure~~
~~Discharged from the hospital~~	~~Rare~~	~~Patients that are discharged from the hospital within 24 hours following matching, without an invasive procedure in the same time frame, will be counted as not having an invasive procedure~~
Exposure to NovoSeven® after time0	*Likely*	*In case a matched control is exposed to NovoSeven® after the matching or an exposed woman have additional doses, this event will be treated according to a treatment policy strategy, i.e. these intercurrent events are ignored in the statistical analysis.*

~~Matching (time0) is defined as 20 minutes after first exposure to NovoSeven® The 20 minute gap is chosen to disregard any case where a conjoint decision have been taken to administer NovoSeven® and perform an invasive procedure consecutively~~.

Timescale for matching is time (in hours and minutes) since onset of sPPH. For exposed women: Time0 is defined as time of first administration of NovoSeven®. It occurs x minutes after onset of sPPH. For matched controls: Time0 is derived from the matching process. It is equal to the period from onset of sPPH to time of first administration of NovoSeven® for the patient for which they are a matched control.

Rationale for the 20 min lag-time

- *A lag-time was implemented based on inputs from experts within this area.*
- *The 20 minutes lag-time is chosen to disregard any case where a conjoint decision has been taken to administer NovoSeven® and perform an invasive procedure consecutively.*
- *It will take 10 min for NovoSeven® to reach peak coagulation ability[32].*
- *Cases where decision to perform invasive procedure is taken simultaneous with administration of NovoSeven®, NovoSeven® would not have had sufficient time to be effective and the procedure is performed with in the lag time, these are avoided to be considered as lack of efficacy of NovoSeven®.*

The influence of the "20 minutes lag" window will be evaluated by supportive endpoints with different options for the time gap, see Section 8.7.2.

The handling of intercurrent events are chosen for the following reasons:

- If a patient dies within 24 hours after matching without the performance of an invasive procedure, the death is considered possible related to the PPH condition and it is assumed that the lack of any invasive procedures performed is due to lack of time. So the patients was is a condition where performance of an invasive procedure would be highly relevant.
- ~~Regarding the case where a patient is discharge from hospital within 24 hours from matching and without any invasive performed, it is assumed likely that everything is now well for the patient. If the patient had been forced to stay at the hospital for the full 24 hours then no invasive procedure would have been necessary to perform.~~

In the way ~~that~~ intercurrent event~~s~~ *of death is* ~~are~~ handled we are making plausible explicit assumptions of what would have happened if these have not occurred. Therefor the approach to handle the intercurrent events have been named a hypothetical strategy. As explicit values are assigned to the primary endpoint the same end result could also be obtained via a composite endpoint strategy.

In case a control is exposed to NovoSeven® after the matching time0 this be ignored following the treatment policy strategy. Any imputation with event in some or all such cases will bias the results under the null hypothesis. Under the alternative hypothesis that the NovoSeven® does have a positive effect this approach will bias the results towards null. The SAP will include a supportive analysis where controls with subsequent exposure to NovoSeven® without event of the primary endpoint are imputed to also have event. Such analysis will serve as a benchmark in the opposite direction. Supplementary analyses will be performed which is detailed in the SAP.

Additional doses with NovoSeven® in the already exposed women will also be ignored following the treatment policy strategy for the same reasons as above. If the null hypothesis is rejected the influence of additional doses will be explored and be part of the evaluation of an appropriate treatment recommendation. Details will be provided in the SAP.

7.3 Secondary objectives

The secondary objectives are:

1. To compare frequency of TEs in women with an event of sPPH treated with NovoSeven® versus women with an event of sPPH not treated with NovoSeven®
2. To compare the relative reduction in blood transfusions in women with an event of sPPH patients treated with NovoSeven® versus women with an event of sPPH not treated with NovoSeven®.
3. To compare the relative reduction in blood loss in women with an event of sPPH patients treated with NovoSeven® versus women with an event of sPPH not treated with NovoSeven®.
4. To compare the incidence of hysterectomy in women with an event of sPPH treated with NovoSeven® to the incidence of hysterectomy in women with an event of sPPH not treated with NovoSeven®.

8 Research methods

8.1 Study design

This is a single-centre, retrospective non-interventional cohort study of women with sPPH who were treated with NovoSeven® or other standard of care, respectively including data from four cohorts of sPPH patients during the period of ~~January 2005~~-*January 2006*-April 2016 (shown in Figure 1). The target population is women with an event of sPPH.

Information regarding patient characteristics, concomitant treatment and outcomes in women with an event of sPPH treated with NovoSeven® is usually limited in many countries. The current study will therefore include a description of women with sPPH treated with NovoSeven®, or standard of care in each of the four cohorts. This will also include an assessment of the comparability of the cohorts and the frequency of clinical outcomes in the study population. To aid in this assessment propensity scores will be calculated and used to match the women with an event of sPPH treated with NovoSeven® and those that are not treated with NovoSeven®.

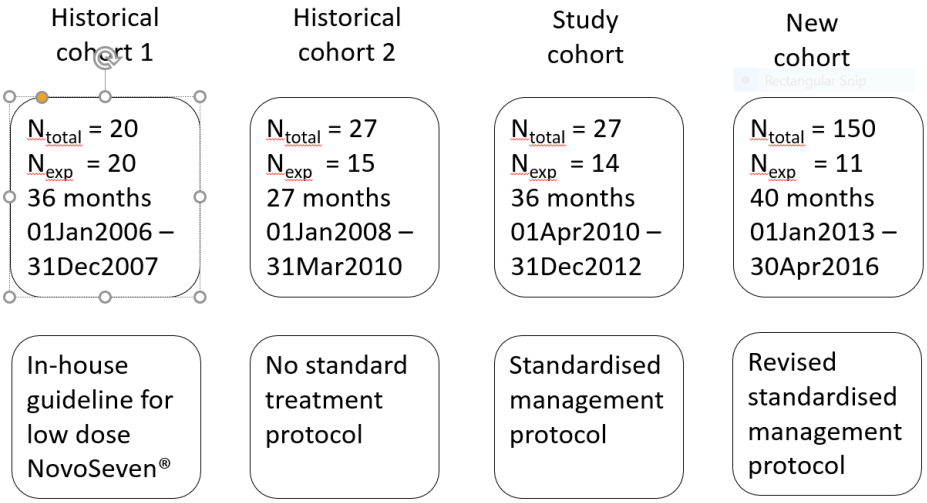

Figure 1 Study design

N_{total}: Total number of sPPH patients. N_{exp}: number of sPPH patients exposed to NovoSeven®. Numbers provided for new cohort is estimations. The naming of the first three cohorts refer to the names used by in the published paper by Colucci et al[7] and the "New cohort" will be added but was not included in the previous publication.

The treatment of sPPH in the four cohorts are briefly described below:

Historical cohort 1

From 01 January ~~2005~~ *2006* to 31 December 2007, all patients with sPPH were treated with uterotonics, fluid management, red blood cells (RBC), fresh frozen plasma (FFP), and/or fibrinogen and platelet (PLT) transfusion according to current practice. If massive bleeding persisted after

transfusion of 8 RBCs and 4 units of FFP, all patients received NovoSeven® at a dose of 60 µg/kg body weight, according to an in-house guideline for treatment of massive bleeding. If blood loss was still ongoing, a second NovoSeven® dose was given. If uncontrollable bleeding persisted after this second dose, hysterectomy was performed [7]. Refer Appendix A for further details.

Historical cohort 2

From 01 January 2008 to 31 March 2010, no specific treatment guidelines were followed. The decision whether and when to administer blood products and haemostatic agents (e.g. TXA, fibrinogen, and NovoSeven®) was left to the discretion of individual team leaders.

Study cohort

All patients aged 18 years or older who developed sPPH after vaginal delivery or caesarean section between 01 April 2010, and 31 December 2012, were treated according to the standardised management protocol depicted in Appendix A. Briefly, identification of PPH initiated the monitoring together with mechanical, and physiological measures to stimulate the uterine contraction. Hereafter, pharmacological measures were followed including early administration of uterotonics, fluids, and TXA. If bleeding persisted, an "emergency package" containing 4 units of RBCs, 4 units of FFP, 1 PLT concentrate, 2 g of fibrinogen concentrate, and NovoSeven® at a dose of 60 µg/kg body weight was given to the patient. Additional NovoSeven® was administered if bleeding persisted. Surgical interventions included the identification and repair of lower genital tract lesions, manual and instrumental uterine revision and curettage, uterine tamponade by a balloon catheter or by surgical towels, laparotomy and uterine compression sutures (B-Lynch or Pereira sutures, Hayman suture technique, square sutures), and uterine artery embolization. More blood products could be given if bleeding persisted. After consulting a haematologist, a third dose of NovoSeven® could be administered. If bleeding still persisted, hysterectomy was performed[7].

New cohort

All patients aged 18 years or older who developed sPPH after vaginal delivery or caesarean section between 01 January 2013 and 30 April 2016, were treated according to the standardised management protocol referred to in Appendix A. Briefly, the treatment protocol was very similar to that for the study cohort; however, the dose of NovoSeven® was changed to 90 µg/kg.

8.1.1 Endpoint(s)

8.1.1.1 Primary endpoint

Endpoint title	Time frame	Unit
Occurrence of invasive procedures (yes/no)	*20 min*-24 hours following time0	Count of women

Timescale for matching is time (in hours and minutes) since onset of sPPH. For exposed women: Time0 is defined as time of first administration of NovoSeven®. It occurs x minutes after onset of sPPH. For matched controls: Time0 is derived from the matching process. It is equal to the period from onset of sPPH to time of first administration of NovoSeven® for the patient for which they are a matched control (8.7.2).~~Time0 will be 20 minutes after the timepoint of first administration of NovoSeven® for the exposed women and the timepoint for their matched controls where they have a propensity score similar to that of the NovoSeven® exposed women.(8.7.3).~~

Invasive procedures are defined as: uterine or iliac artery ligation, radiological arterial embolisation, uterine compression sutures, or hysterectomy

8.1.1.2 Secondary endpoints

Endpoint title	Time frame	Unit
Occurrence of thromboembolic events, yes/no	From time0 until 5 days after time0	Count of woman
Amount of blood products transfused	From delivery to 24h after time0	Units
Estimated blood loss	From delivery to 24h after time0	mL
Occurrence of hysterectomy, yes/no	*20 min*-24 hours following time0	Count of woman

Timescale for matching is time (in hours and minutes) since onset of sPPH. For exposed women: Time0 is defined as time of first administration of NovoSeven®. It occurs x minutes after onset of sPPH. For matched controls: Time0 is derived from the matching process. It is equal to the period from onset of sPPH to time of first administration of NovoSeven® for the patient for which they are a matched control (8.7.2).~~time0 will be 20 minutes after the timepoint of first administration of NovoSeven® for the exposed women and the timepoint for their matched controls where they have a propensity score similar to that of the NovoSeven® exposed women.(8.7.3).~~

8.1.2 Treatment of patients

The women included in the study population have been treated according to local routine clinical practice at the discretion of the treating physician. All data are evaluated retrospectively.

8.2 Setting

8.2.1 Study population

The study population will consist of women fulfilling the inclusion criteria. Expected size of the study population is shown in section 8.5.

8.2.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered “yes”.

1. Females
2. sPPH, defined as continuous bleeding of more than 1500 mL within 24 hours after delivery
3. Inclusion in one of the four cohorts (historical cohort 1, historical cohort 2, study cohort and new cohort)

The cohorts are described in section 8.1.

8.2.3 Exclusion criteria

There are no exclusion criteria

8.2.4 Rationale for selection criteria

The inclusion criteria are chosen as the focus of the study is sPPH which can only happen in females and data are available for analyses. As all women with an event of sPPH treated at University Hospital of Bern should be available for the analysis, the women are representative for the source population which is the women with an event of sPPH treated at the University of Bern.

8.2.5 Withdrawal criteria

It is not possible to withdraw from the study as data is already collected and will be transferred anonymised to Novo Nordisk for analysis. Furthermore, study population has already been treated and cannot withdraw.

8.2.6 Visit procedures

This is a retrospective study of women treated for sPPH during standard clinical practice during the period the 01-Jan-~~2005~~ *2006* to 30-Apr-2016.

Data will be extracted from patient charts, anaesthesiology records and transfusion records.

The data included in the study will cover the period from time of diagnosis of sPPH (including baseline data) until the end of hospitalisation.

There will be no study specific visits.

8.3 Variables

Variables collected from patient charts will include:

- maternal age intervals (<20, 21-25, 26-30, 31-35, 36-40, >40 years)
- weight (kg)
- parity
- gravidity
- gestational age at birth (weeks)
- estimated total blood loss (mL) until sPPH stop, discharge from hospital or death
- risk factors predisposing to PPH

- mode of delivery (spontaneous vaginal, instrumental vaginal or grade I or II caesarean section)
- cause of PPH
- infused non-blood product fluids (mL or units)
- blood product replacement (mL or units)
- medicinal and surgical treatments
- duration of bleeding prior to administration of haemostatic agents, including NovoSeven® (min)
- stay in intensive care unit (ICU), (yes/no)
- length of hospitalisation after delivery (days)
- postpartum hysterectomy (yes/no)
- TEs (yes/no), measured during the time of hospitalisation~~s~~
- death (yes/no), measure during the time of hospitalisation~~s~~
- cause of death

These variables will be supplemented with time information of medical treatment, invasive procedure, and transfusions. The supplementary information will be extracted from electronic anaesthesiologist records.

These supplementary variables will include:

- time, name, and dose of bolus drugs (including haemostatic agents and uterotonics)
- time, name, and dose of other drugs (p.o., rectal etc, including haemostatic agents and uterotonics)
- time, name, and volume of fluid expansion and transfusions
- time and volume of blood loss
- time and type of invasive procedures

8.4 Data sources

Data originates from original database collected by Colucci et al. as described in the publication [7]. These data were analysed together with the supplemental data from women in the new cohort collected retrospectively from electronic medical records. Furthermore, for women included in the study published by Colucci et al [7], additional information on timing of different interventions will be collected. As described in the published study [7], the medical record of all women with an event of sPPH were analysed for the clinical data of interest documented by the treating physician(s) or nurse(s)/midwife(s). The women were followed until hospital discharge. The clinical data were collected in a dedicated database.

8.4.1 Data quality

All publication data were collected from the medical record of the women that met the inclusion criteria. Three Authors of the Colucci et al [7] paper (Helsing K, Schmid P, and Colucci G) collected

the data from the records. One Author (Colucci G) checked for correctness and accuracy of data for all women.

8.5 Study sample size

The Table below show the expected number of women to be included in the data source.

Table 2 Sample size per cohort

Cohort*	Number of women with an event of sPPH treated with NovoSeven®	Number of women with an event of sPPH not treated with NovoSeven®	Total number women with an event of sPPH
Historical cohort 1	20	0	20
Historical cohort 2	15	12	27
Study cohort	14	13	27
New cohort[+]	10	140-190	150-200

*Please see Figure 1 for explanation of the naming of cohorts, [+]Approximate numbers

8.6 Data management

Novo Nordisk will provide a data collection excel sheet for capture of study specific data. Instructions for completion and correction of the data collection sheet will be provided. The physician will ensure that study specific data is entered in the data collection sheet according to agreed timelines and that data are complete and accurate.

Appropriate measures such as encryption and anonymisation/pseudonymisation must be enforced to protect the identity of patients when transmitting data, in all presentations and publications as required by local/regional/national requirements.

An audit trail will be maintained in a log including identification of the person entering the data, date and time of the entry and reason for the correction, the original entry and the corrected entry.

By signing the affirmation statement, the physician confirms that the information in the data collection sheet is complete and correct.

If corrections are made by the physician's authorised staff after the date of the physician's signature on the affirmation statement, this must be signed again by the physician.

Data will be collected at Bern University hospital and hereafter transferred to Novo Nordisk.

Data will be blinded. The details of blinding will be added in the data management plan.

8.7 Data analysis

8.7.1 Summary of previous published results

Colucci et al [7] previously published results that included the study cohort and the two historical cohorts. They analysed the differences between the three cohorts and concluded that it is beneficial to use a standardised management protocol when treating PPH. Furthermore, the study suggested that such a management protocol should include uterotonics and immediate administration of TXA, transfusion of RBC, FFP and PLT concentrates, and thereafter administration of low-dose fibrinogen concentrate and NovoSeven®. These measures were shown to reduce blood product administration and rate of emergency hysterectomy in women with an event of sPPH. Of all 74 women included in the study, 1 (1.4%; patient from the historical cohort 2) experienced a pulmonary embolism diagnosed on day 10 after delivery. The patient did neither receive TXA, fibrinogen nor NovoSeven®. There were no maternal deaths. They concluded that early aggressive treatment of sPPH with a coordinated multifunction team is the best option.

8.7.2 Definition of analysis sets

All women who meet the inclusion and eligibility criteria for the study, will be included in the full analysis set.

8.7.3 Statistical methods

8.7.3.1 Analysis of primary endpoint

The primary objective will be answered using propensity score matching to ensure exchangeability between sPPH patient treated with NovoSeven® and those that are not across all 4 cohorts. These analyses will be addressed using data from the patient`s electronic record that includes timing of variables.

For exposed women: Time0 is defined as time of first administration of NovoSeven®. It occurs x minutes after onset of sPPH. For every exposed woman, all unexposed and eligible women are evaluated at this time=time0. The ones with similar propensity score are selected for matching (up to four will be selected). Thus, for unexposed women (matched controls): Time0 is the timepoint used when they were selected for matching. It is equal to the period from onset of sPPH to time of first administration of NovoSeven® for the patient for which they are a matched control. In this way exposed and unexposed women and comparable because they have similar propensity score at the same (specific) Time0.

Propensity score matching will be performed to ensure equitable comparability between women with an event of sPPH being exposed to NovoSeven® with women with an event of sPPH that are not at the matching timepoint. In this approach, the propensity score will reflect the estimated probability of being administered with NovoSeven® during the course of severe PPH. A propensity score for every woman with sPPH will be estimated by an appropriate analytic model with

NovoSeven® as the dependent variable. Covariates associated with initiation of NovoSeven® administration will be included in a model to calculate propensity scores. Characteristics considered to be potential confounders for the association between use of NovoSeven® and the outcome or characteristics considered to be risk factors for the occurrence of the primary outcome measure alone will be included as covariates in the propensity score model [33].

Data will be transferred to Novo Nordisk in the two parts. Part one will include data needed for the propensity score matching whereas part two will include outcome data (primary and secondary endpoints).

Characteristics that could be included as covariates are (not an exhausted list): gestational age, multiple pregnancy, cause of PPH, volume of blood loss at time of intervention, and haemostatic drugs used (other than NovoSeven®) that had already been applied at the time of intervention. A matching algorithm for the propensity score will be used to match women with an event of sPPH exposed to NovoSeven® with women with an event of sPPH that are not at that timepoint. Women will be censored when they have been hysterectomised, dies, or stopped having PPH. Further details of the propensity score model will be defined in the SAP.

Matching will be done within patients with the same delivery mode with up to 1:4 matching with a calliper of 0.1. If this is not possible a calliper of 0.2 will be used instead. The criteria for switching to 0.2 will be described in the SAP.

The primary endpoint (invasive procedures) will be compared between women who are managed by NovoSeven® and those that are not, using an *exact conditional* logistic regression to calculate the odds ratio, with a 95% confidence interval (95% CI) based on the propensity score matching. The test will be two sided and assessed at the 5% significant level.

Missing values due to discharge from hospital within 24 hours following matching, without an invasive procedure in the same time frame, will be counted as not having an invasive procedure. The rationale for this decision is that a patient without any invasive procedures would most probably not have been discharged from hospital within 24 hours following matching if she still needed further treatment.

~~To evaluate the robustness of the study findings and the impact of using propensity score-matching, a supportive analysis will be performed of the primary outcome measure by including the propensity score as a covariate in a logistic regression model estimating the odds ratio between exposed and non-exposed women with an event of sPPH.~~

Supportive analyses:

Additional analyses of the primary endpoint will be done based on two subgroups of women having and not having invasive procedures before matching.

To evaluate the robustness of the study findings and the impact of using propensity score-matching, a supportive analysis will be performed of the primary outcome measure by including the propensity score as a covariate in a logistic regression model *to compare the primary outcome measure between both exposed and non-exposed PPH patients, under the assumption that the propensity score has a linear functional relation with the log odds of the primary outcome. This will be done for the primary population (the matched women).*

To evaluate the effect of the 20 min lag time in the primary endpoint, alternative endpoints will be analysed to evaluate the impact of this definition. These "sensitivity endpoints" will be made for the following lag times: a) 10 min – 24h following time0 and b) 30 min – 24h following time0. For further details see the SAP.

~~Further details on the statistical analyses will be described in the Statistical analysis plan (SAP).~~

8.7.3.2 Analysis of secondary endpoints

To answer the secondary objectives, the comparisons will be made using the matched women from the propensity score matching described above. A significance level (alpha) of 0.05 will be used.

The statistical analyses are briefly described below, more details will be provided in the SAP.

Frequency of TEs:

The first secondary objective is to compare frequency of TEs (in total and separate for venous and arterial) in women with an event of sPPH treated with NovoSeven® versus women with an event of sPPH not treated with NovoSeven®.

In the analyses will be included the population matched in the propensity score matching. The frequencies will be compared using Fisher's exact test.

Control of bleeding

The two secondary objectives related to control of bleeding in women with an event of sPPH patients treated with NovoSeven® versus women with an event of sPPH not treated with NovoSeven®. To fulfil these objectives two endpoints will be used:

1. Amount of blood products transfused
2. Estimated blood loss

Both endpoints will be reported and evaluated by comparing the relative change pre-post time0 between the two groups of patients together with a comparison of the post time0 levels.

The total number of blood products units will be analysed using a negative binomial regression with treatment, period (pre/post time0), the interaction between treatment and period as factors. The

propensity score will be included as a covariate in the model. Subject will be included as a random effect, and (log)duration of each period will be included as an offset. The interaction term will give a statistical test for difference in the relative change in blood product use pre and post time0 between the two groups.

The total estimated blood loss from each patient and each period will be analysed with a log-linear regression model with treatment, period (pre/post time0), the interaction between treatment and period as factors. The propensity score and (log)duration of each period will be included as covariates in the model. Subject will be included as a random effect. The interaction term will give a statistical test for difference in the relative change in estimated blood loss pre and post time0 between the women with an event of sPPH treated with NovoSeven® and their matched controls.

This will be repeated comparing the post time0 levels.

Hysterectomy:
The fourth objective is to compare the incidence of hysterectomy in women with an event of sPPH treated with NovoSeven® to the incidence of hysterectomy in women with an event of sPPH not treated with NovoSeven®. The comparison of the incidences will be analyses using a conditional logistic regression model. ~~same method as for the primary endpoint.~~

8.7.3.3 Analysis of exploratory endpoints

Several exploratory analyses will be conducted. These will be described in the SAP.

8.8 Quality control

All data for the publication were searched in the medical record of the women that meet the inclusion criteria. Three Authors of the Colucci et al [7] paper (Helsing K, Schmid P, and Colucci G) collected the data from the records. One Author (Colucci G) checked for correctness and accuracy of data of all women. Data collected for the new cohort will be collected by a study midwife and an obstetrician. The latter will check for correctness and accuracy of the data.

8.8.1 Critical documents

Before the physician starts the study ~~(which is when informed consent is obtained from the first patient)~~, the following documents must be available to Novo Nordisk:

- Data transfer agreement
- Signed and dated agreement on the final protocol
- Approval/favourable opinion from Bern University Hospital Independent Ethics Committee (IEC) of the study

8.8.2 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiology Practice (GPP) and relevant national legislation related to archiving of study documentation.

The physician must agree to archive the documentation pertaining to the study in an archive for at least 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Novo Nordisk.

Novo Nordisk will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

8.9 Limitations of the research methods

As this is a non-interventional study, potential confounding factors cannot be ruled out. Data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation.

An observational study cannot replicate the design and results of a placebo-controlled randomised clinical trial since neither randomisation nor placebo treatment are part of clinical practice. An observational study will compare against a comparator; in this case standard of care (comparative effectiveness) and PPH severity, as well as preferences of treating physician may influence the choice of treatment. This confounding by indication may introduce differences between the groups to be compared regarding patient characteristics associated with the treatment choice, as well as the outcome. This is referred to as confounding by indication, or channelling bias. This is a major potential source of bias in comparative effectiveness studies that needs to be taken into account in the design as well as the analyses and interpretation of the study findings. Women with PPH is a heterogeneous patient population with multiple treatment options.

Other limitations could include information bias (potential measurement error of exposure [such as dose µg/kg and frequency] and outcomes [internal validity of outcomes such as procedure and control of bleeding) and selection bias (selection into the study and also generalizability).

Data will be collected at different time period which might introduce confounders. As an example, the estimation of blood loss is collected more precisely in the study cohort than in the other cohorts. This fact together with the skewed distribution of women from the cohorts in each subgroup based on TXA/NovoSeven® use might introduce a confounder as the study cohort have been managed according to a standardised protocol that include many other elements than TXA and NovoSeven®.

9 Protection of human subjects

The study will be conducted in accordance with GPP [34].

9.1 Informed consent form for study patients

No informed consent needed for this study according to local regulations.

9.2 Data handling

Anonymised data will be transferred to Novo Nordisk A/S where analyses described in this protocol outline will be carried out.

9.3 Institutional Review Boards/Independent Ethics Committee, health authorities and other relevant national institutions/bodies

Study specific documentation (study protocol) must be submitted to the relevant national bodies as required by national regulation and procedures in the participating countries.

9.4 Premature termination of the study

The sponsor may decide to stop the study or part of the study at any time.

10 Management and reporting of adverse events/adverse reactions

This study is based on secondary use of data and therefore ~~no reporting of adverse events/reactions will be performed~~ *Individual Case Safety Report will not be performed* [35].

11 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk for regulatory purposes and for the safety surveillance of NovoSeven®. All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk.

11.1 Registration of study information

In accordance with Novo Nordisk's commitment to transparency in clinical activities, this study will be registered on `ClinicalTrials.gov´ and www.novonordisk-trials.com prior to the first capture of data.

11.2 Communication and publication

Novo Nordisk commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

It is planned to publish the outcome of the study described in this protocol in a separate publication and to combine the results from the study described in this protocol with results from studies of other data sources described in separate protocols with a similar aim to make a combined publication. The data collectors, physicians, and data contributors will be authors on both publications following international publication guidelines.

At the end of the study, one or more publication(s) may be prepared by physician(s) in collaboration with Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property and reserves the right not to release interim results or data until a study report is available. The results of this study will be subject to public disclosure on external websites according to international regulations, as reflected in the Novo Nordisk Commitment to share information about clinical studies.

The physician must ensure submission of the results of the study (either abstracts or full study report) to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the

relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication.

11.3 Physician access to data and review of results

As owners of the study database, Novo Nordisk has discretion to determine who will have access to the database.

Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or product studied in this study.

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Appendix A

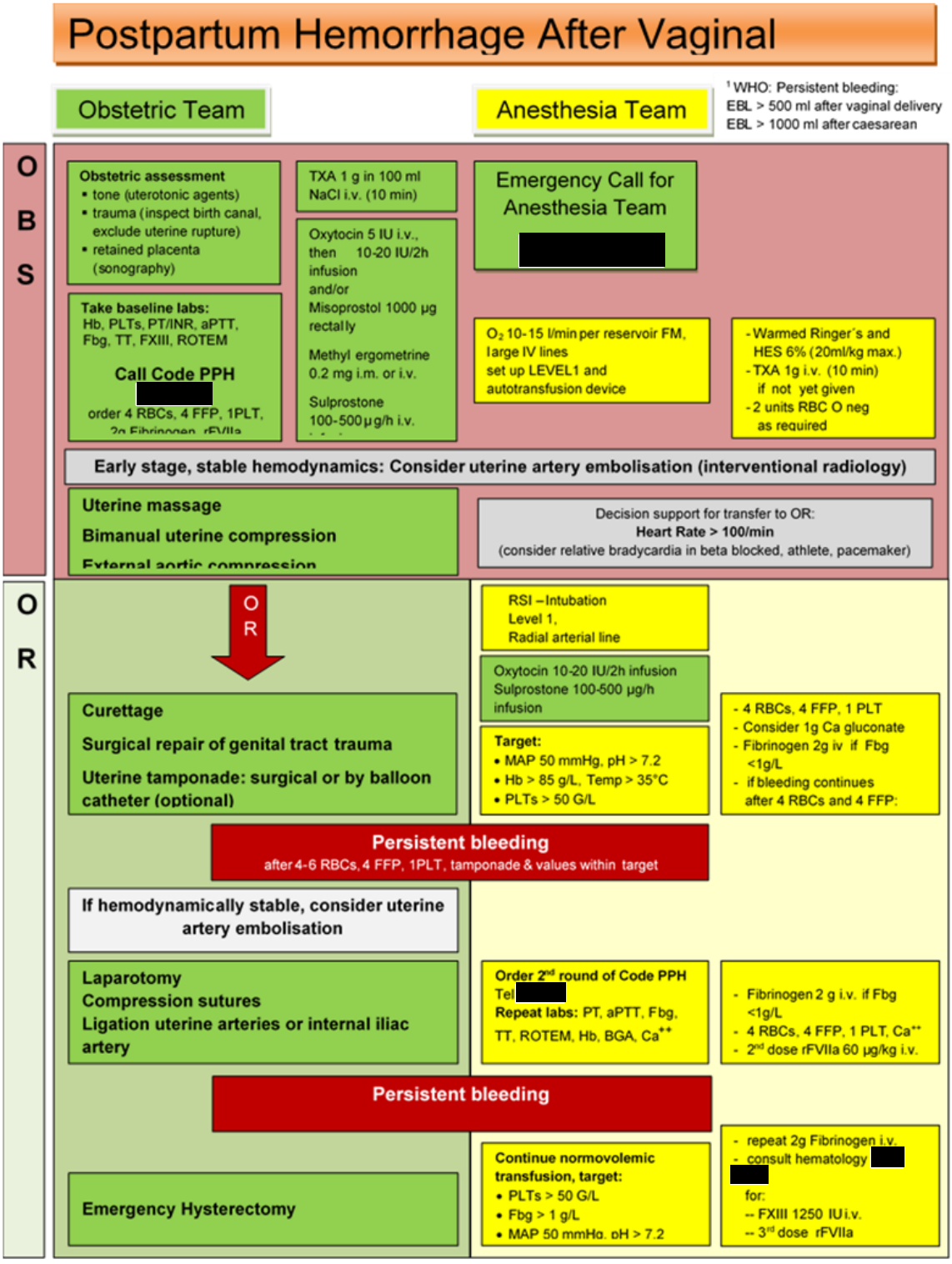
Treatment protocols for cohorts

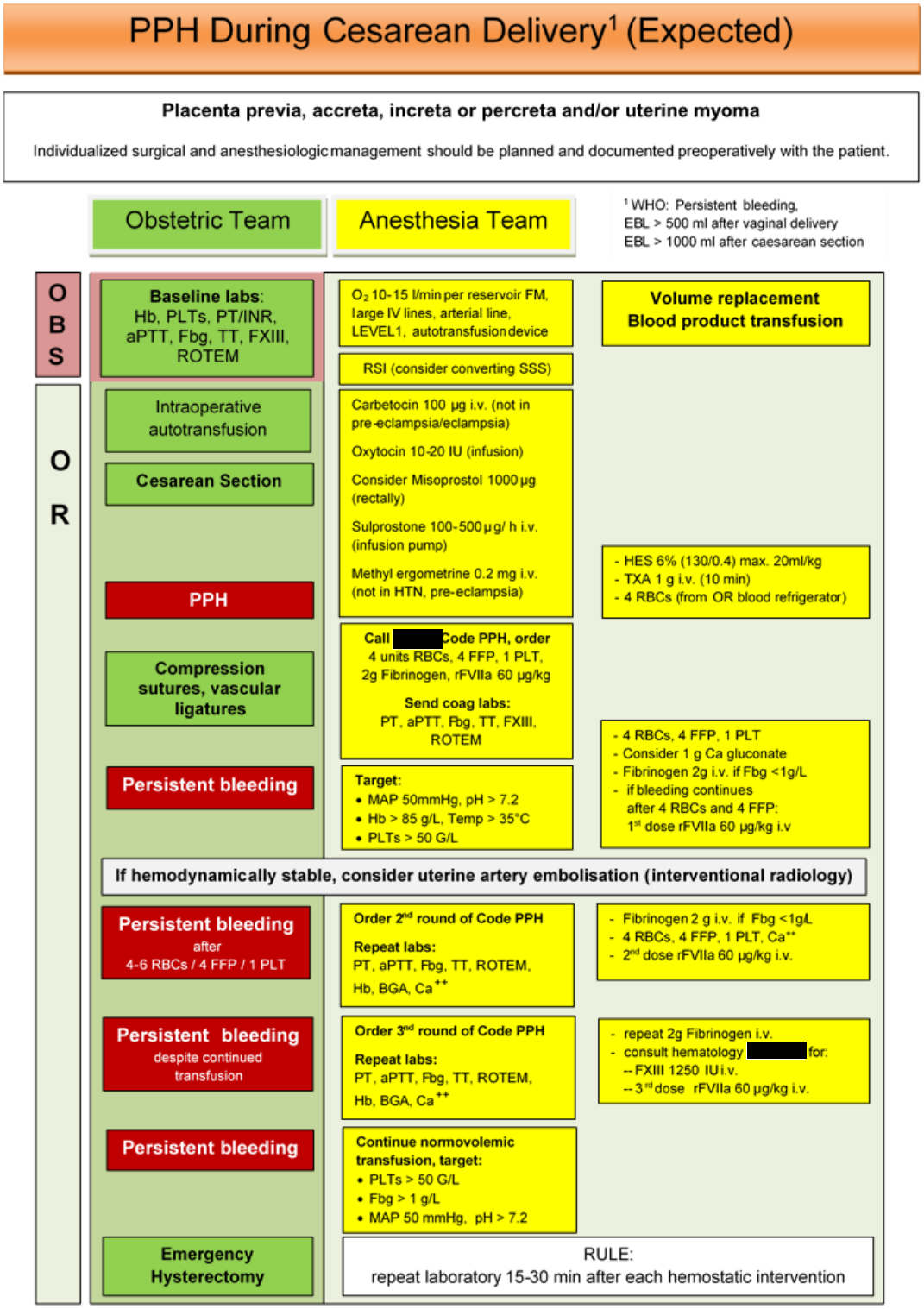
New cohort

Treatment protocol is described in: Peripartum Haemorrhage, Diagnosis and Therapy. Guideline of the DGGG, OEGGG and SGGG (S2k Level, AWMF Registry No. 015/063, March 2016) [31]

DGGG: German Society of Gynaecology and Obstetrics
OEGGG: Austrian Society of Gynaecology and Obstetrics
SGGG: Swiss Society of Gynaecology and Obstetrics

Study cohort




PPH During Cesarean Delivery[1] (Expected)
Placenta previa, accreta, increta or percreta and/or uterine myoma
Individualized surgical and anesthesiologic management should be planned and documented preoperatively with the patient.
Obstetric Team
Anesthesia Team
[1] WHO: Persistent bleeding,
EBL > 500 ml after vaginal delivery
EBL > 1000 ml after caesarean section
OBS
OR
Baseline labs: Hb, PLTs, PT/INR, aPTT, Fbg, TT, FXIII, ROTEM
O2 10-15 l/min per reservoir FM, large IV lines, arterial line, LEVEL1, autotransfusion device
Volume replacement
Blood product transfusion
RSI (consider converting SSS)
Intraoperative autotransfusion
Carbetocin 100 µg i.v. (not in pre-eclampsia/eclampsia)
Oxytocin 10-20 IU (infusion)
Consider Misoprostol 1000 µg (rectally)
Sulprostone 100-500 µg/ h i.v. (infusion pump)
Methyl ergometrine 0.2 mg i.v. (not in HTN, pre-eclampsia)
Cesarean Section
PPH
- HES 6% (130/0.4) max. 20ml/kg
- TXA 1 g i.v. (10 min)
- 4 RBCs (from OR blood refrigerator)
Call [redacted] Code PPH, order
4 units RBCs, 4 FFP, 1 PLT, 2g Fibrinogen, rFVIIa 60 µg/kg
Send coag labs: PT, aPTT, Fbg, TT, FXIII, ROTEM
Compression sutures, vascular ligatures
Persistent bleeding
Target:
• MAP 50mmHg, pH > 7.2
• Hb > 85 g/L, Temp > 35°C
• PLTs > 50 G/L
- 4 RBCs, 4 FFP, 1 PLT
- Consider 1 g Ca gluconate
- Fibrinogen 2g i.v. if Fbg <1g/L
- if bleeding continues after 4 RBCs and 4 FFP: 1st dose rFVIIa 60 µg/kg i.v
If hemodynamically stable, consider uterine artery embolisation (interventional radiology)
Persistent bleeding after 4-6 RBCs / 4 FFP / 1 PLT
Order 2nd round of Code PPH
Repeat labs: PT, aPTT, Fbg, TT, ROTEM, Hb, BGA, Ca++
- Fibrinogen 2 g i.v. if Fbg <1g/L
- 4 RBCs, 4 FFP, 1 PLT, Ca++
- 2nd dose rFVIIa 60 µg/kg i.v.
Persistent bleeding despite continued transfusion
Order 3rd round of Code PPH
Repeat labs: PT, aPTT, Fbg, TT, ROTEM, Hb, BGA, Ca++
- repeat 2g Fibrinogen i.v.
- consult hematology [redacted] for:
-- FXIII 1250 IU i.v.
-- 3rd dose rFVIIa 60 µg/kg i.v.
Persistent bleeding
Continue normovolemic transfusion, target:
• PLTs > 50 G/L
• Fbg > 1 g/L
• MAP 50 mmHg, pH > 7.2
Emergency Hysterectomy
RULE:
repeat laboratory 15-30 min after each hemostatic intervention

Historical cohort 1

Topic		Comment
Information	Contact	Early contact with haematologist on call
	Diagnostics	Surgical bleeding?
		Coagulation disorder that can be targeted?
		Anticoagulant drug that can be antagonized?
		Acquired coagulopathy?
		Acidosis?
	Laboratory	Haemoglobin?
		Platelet count?
		Coagulation tests?
		Draw blood for coagulation tests before rFVIIa
	Treatment already given	Number of blood products (RBC, FFP, PLT)?
		TXA ?
		Haemostatic drugs (DDAVP, vWF/FVIII, Fibrinogen, Fibrin glue)?
		Surgery?
Preconditions	Inclusion criteria	Persistent severe bleeding (i.e. ≥ 4 mL/kg/h) after 8 RBC and 4 FFP units
		Exclusion of an otherwise treatable bleeding
		Optimal treatment with blood products, haemostatic drugs, and surgery
		Platelet count > 20 x10^9/L
	Exclusion criteria	Patient with a non-treatable and likely pre-terminal condition, such as non-treatable metastatic cancer, severe liver cirrhosis without indication for liver transplantation, very severe traumatic brain injury, pre-terminal chronic disease
	Absolute contraindications	Non-compensated DIC or severe sepsis
		Acute myocardial infarction
		Acute ischemic cerebral stroke
	Relative contraindications	Severe coronary heart disease
		Previous ischemic cerebral insult
	Antifibrinolytic drug	The use of an antifibrinolytic drug like TXA is recommended before the use of rFVIIa
Dosing	Haematologist consultation	No rFVIIa without consultation
	First dose	60 µg/kg body weight iv [36, 37]
	Second dose	Repeat same dose after 60 to 120 minutes if the bleeding persists but has decreased; in case of unchanged bleeding a repeat dose of 90 µg/kg body weight is allowed
	Third dose	No third dose is advised [38]
Follow-up	Laboratory	Obtain blood sample for coagulation tests 1 h and 12 h after use
	Documentation	Return completed data sheet with clinical data

Abbreviation: TXA- Tranexamic acid

Historical cohort 2

No protocol for management of sPPH were available and thus it was left to the discretion of the treating health care professional to find the right way to management the bleeding.

ANNEX 1. List of Stand-alone Documents

List of Stand-alone Documents

Number	Document reference number	Date	Title
1			Data Transfer agreement

List of figures and tables

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