Observational Plan ("Study Protocol") for Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions

Post-Authorisation Safety Study (PASS) Information

Title	Retrospective, Multinational, Drug Utilisation Study (DUS) to Investigate the Routine Use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in HES-Accredited European (EU) Hospitals after Implementation of a Set of Risk Minimisation Measures
Study Identifier	HE06-027-CNI
Observational Plan Version Identifier	Final 2.0
Date of Last Version of Observational Plan	09 Sep 2019
EU PAS Register Number	Will be added after finalisation of the observational plan ("study protocol") and its approval by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency
Active Substances	ATC Code: Blood substitutes and plasma protein fractions B05AA07 hydroxyethyl starch Active pharmaceutical ingredients: HES 130/0.4 HES 130/0.42
Medicinal Products	Fresenius Kabi Deutschland GmbH: The registered product name for the individual products concerned in the European countries in which the DUS will be conducted is provided in Annex 1a. B. Braun Melsungen AG: The registered product name for the individual products concerned in the European countries in which the DUS will be conducted is provided in Annex 1b.

Product Reference	Not applicable
Procedure Numbers	Fresenius Kabi Deutschland GmbH: EMEA/H/N/PSP/J/0067.1 B. Braun Melsungen AG: Same number as for Fresenius Kabi due to joint procedure
Marketing Authorisation Holders (MAH) / Study Sponsor	Marketing Authorisation Holders: Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany B. Braun Melsungen AG Carl-Braun-Straße 1 34212 Melsungen, Germany Study Sponsor: Fresenius Kabi Deutschland GmbH Else-Kröner-Straße 1 61352 Bad Homburg v.d.H., Germany
Joint PASS	Yes
Research Question and Objectives	The primary objective of the imposed DUS is to assess the non-adherence of physicians in HES-accredited hospitals to the approved European Product Information [regarding indication for use, contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures. This allows to evaluate the effectiveness of these measures.

Countries of Study	It is intended to conduct the study in a representative sample of European Union member states like Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, The Netherlands, etc. Final country selection will be based on the feasibility survey, non-adherence rates of the first HES DUSs (ENCePP Register No.: EUPAS10897, EUPAS12540), HES 130 sales figures and the willingness of HES-accredited hospitals to participate in this DUS.
Authors	[redacted]

Marketing Authorisation Holders

Marketing Authorisation Holders	**Fresenius Kabi Deutschland GmbH** Else-Kröner-Straße1 61352 Bad Homburg v.d.H., Germany **B. Braun Melsungen AG** Carl-Braun-Straße 1 34212 Melsungen, Germany
MAHs Contact Persons / Sponsor Contact Person	[redacted]

1 Table of Contents

List of Figures

2 List of Abbreviations

ADR	Adverse Drug Reaction
AG	Aktiengesellschaft (incorporation)
ATC	Anatomic Therapeutic Chemical classification
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - human
CRF	Case Report Form
CRO	Contract Research Organisation
DUS	Drug Utilisation Study
EC	European Commission
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
e.g.	Exempli gratia, example given
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	EU electronic register of post-authorisation studies
GmbH	Gesellschaft mit beschränkter Haftung (limited liability company)
GVP	Good Pharmacovigilance Practice
HES	Hydroxyethyl Starch
i.e.	Id est, that is
IEC	Independent Ethics Committee
ICU	Intensive Care Unit
ISPE	International Society of Pharmacoepidemiology
kg	Kilogramme
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
ml	Millilitre
No.	Number
PASS	Post-authorisation safety study
PDMS	Patient Data Management System
PI	Product Information
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
QPPV	Qualified Person for Pharmacovigilance
RRT	Renal Replacement Therapy
SOP	Standard Operation Procedure

3 Responsible Parties

The **sponsor** of this DUS is the MAH Fresenius Kabi Deutschland GmbH (Else-Kröner-Straße 1, 61352 Bad Homburg v.d.H., Germany).

The sponsor Fresenius Kabi Deutschland GmbH will jointly conduct this DUS in collaboration with the concerned MAH B. Braun Melsungen AG (collaborator).

Contact persons for each MAH:

[redacted]

Cooperation between these MAHs regarding the DUS will be contractually fixed. The sponsor will monitor the progress of the DUS and receive status reports from the CRO concerning e.g. the number of documented patients.

A **Contract Research Organisation (CRO)** will provide all logistical and regulatory support for the study, observe data quality, host the database, analyse the data and write the final study report. Further details about the respective task allocation between the two MAHs and the CRO are defined in a task allocation list which is part of the contract with the CRO.

[redacted]

A **principal investigator** for each site will be assigned before the first patient will be documented in the DUS in the respective country. If required by national law or regulations, a **coordinating investigator** in participating countries will be additionally assigned. Contact details and a list of all investigators and participating hospitals will be kept in a stand-alone document (see Annex 1c).

4 Abstract

Title
Retrospective, Multinational, Drug Utilisation Study (DUS) to Investigate the Routine Use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in HES-Accredited European (EU) Hospitals after Implementation of a Set of Risk Minimisation Measures

Observational Plan Version
Final 2.0

Date of the Observational Plan
09 Sep 2019

Main Authors
[redacted]

Rationale and Background
The concerned Marketing Authorisation Holders (MAHs) have been requested by the European Medicines Agency (EMA) to implement a set of risk minimisation measures as outcome of a regulatory procedure for HES solutions (European Commission decision dated 17 Jul. 2018). This includes for instance implementation of a Controlled Access Programme to ensure that HES solutions are only delivered to accredited hospitals where healthcare professionals expected to prescribe/administer these medicinal products have been trained on their appropriate use.

Since the MAHs of HES solutions shall perform a DUS to assess the effectiveness of the set of risk minimisation measures, this study will be conducted.

Research Question and Objectives
The primary objective of the DUS is to assess the non-adherence of physicians in HES-accredited hospitals to the approved European Product Information (PI) [regarding indication for use and the contraindications and posology (dosage)] for HES 130 solutions in clinical routine after implementation of a set of risk minimisation measures. This allows to evaluate the effectiveness of these measures.

Study Design
Retrospective, non-interventional, multinational, European DUS

Population
Patients treated with HES 130 solutions of the concerned MAHs in HES-accredited hospitals after implementation of a set of risk minimisation measures.

Variables

Primary Variable:

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 solutions, the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology).

Variables to be Documented:

- Hospital information including date of initial hospital accreditation, type of hospital, pseudonymised unique patient identifier, patient's hospital admission and discharge date, demographics, prehospital field (before admission to the study hospital: crystalloid used, HES 130 used)
- Indication for HES use at start time of first HES infusion within a prescription, contraindications at start time of HES infusion within a prescription, crystalloid use prior to first HES 130 prescription and/or concomitantly, trade name of any prescribed HES 130 product, hospital ward in which the HES 130-prescribing physician was employed, dosage (posology), main medical procedure the patient underwent

Data Sources

Data will be collected retrospectively from charts of patients treated previously with HES 130. All data will be pseudonymised.

Study Size

The sample size calculation is based on the primary statistical unit of the study: Patients treated with HES 130. For potential non-adherence rates of 5 % to 95 % and aiming for a precision (defined as the confidence interval width) of up to 5 percent points of the exact two-sided 95% confidence interval (according to Clopper-Pearson) for the evaluation of non-adherence, a sample size of 1574 patients is required. To compensate for potential inconclusive cases regarding indication or missing data regarding posology (assumption of 10 %), 1749 patients will be documented.

In case the intended targeted sample size of 1749 could not be reached in the documentation period, analysis with a sample size of 1220 (including 10 % compensation for inconclusive regarding indication or missing data regarding posology) will be performed to ensure a precision (confidence interval width) of at least 6 percent points.

However, the sponsor will make any effort to reach the intended target sample size of 1749.

Data Analysis
Due to the exploratory character of this study only descriptive statistics will be used for the analysis of the variables.

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 solutions, the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology). The full analysis set will comprise all eligible patients.

Furthermore, analysis of non-adherence will also be conducted for each single HES 130 prescription as statistical unit for assessment as secondary measure.

Estimated Milestones

Milestone	Planned date
Start of data collection[a]	31 Oct. 2019 (extrapolated)
End of data collection[b]	31 Dec. 2019 (extrapolated)
Registration in the EU PAS Register	The DUS will be registered in the EU electronic register of post-authorisation studies (EU PAS Register) after final observational plan approval by the PRAC[*] and before the start of data collection.
Final report of study results	16 Jul. 2020 (according to European Commission implementing decision for HES 130-containing medicinal products of 17 Jul. 2018)

[a] Date on which the data extraction from patient charts begins

[b] Date from which the analytical data set is completely available

The dates for start of data collection and end of data collection have been extrapolated based on CMDh's[#] request to submit the study report within 24 months of the European Commission decision of 17 Jul. 2018. These dates will depend on e.g. observational plan approval, implementation period of requested risk minimisation measures, the number of available HES-accredited hospitals, the number of HES 130-treated patients, the number of physicians, CRO selection, eCRF generation, hospital selection, contract negotiations, and physicians' availability.

[*] Pharmacovigilance Risk Assessment Committee

[#] Coordination Group for Mutual Recognition and Decentralised Procedures - human

5 Amendments and Updates

In case of substantial amendments of the study protocol, those will be aligned with Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA).

Number	Date	Section (s) of study protocol	Amendment or update	Reason
1	09 Sep 2019	-PASS Information -3 Responsible Parties -4 Abstract -9.2.1 Countries, Feasibility and Site Selection -Annex 1a -Annex 1b	Amendment	Administrative changes: - New version and date of study protocol/observational plan - Procedure number added - Countries in which study is intended to be performed updated - Department name and title of authors updated - Names and functions of Fresenius Kabi contact persons updated - CRO name and contact details added - HES 130-containing products for added countries added

6 Estimated Milestones

Milestone	Planned date
Start of data collection[a]	31 Oct. 2019 (extrapolated)
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Registration in the EU PAS Register	The DUS will be registered in the EU electronic register of post-authorisation studies (EU PAS Register) after final study protocol approval by the PRAC and before the start of data collection.
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[a] Date on which the data extraction from patient charts begins

[b] Date from which the analytical data set is completely available

The dates for start of data collection and end of data collection have been extrapolated based on the CMDh's request to submit the study report within 24 months of the European Commission (EC) decision of 17 Jul. 2018. These dates will depend on e.g. study protocol approval, implementation period of requested risk minimisation measures, the number of available HES-accredited hospitals, the number of HES 130-treated patients, the number of physicians, CRO selection, eCRF generation, hospital selection, contract negotiations, and physicians' availability.

7 Rationale and Background

Following the publication of investigator initiated clinical trials such as 6S (Perner et al. 2012)[1], CHEST (Myburgh et al. 2012)[2] and VISEP (Brunkhorst et al. 2008)[3], comparing HES-containing solutions with crystalloids in critically ill patients (e.g. septic patients), the EMA imposed in 2013 risk minimisation measures such as restrictions in use of HES products as specified in the European Product Information (Summary of Product Characteristics, package leaflet).

The results of two drug utilisation studies (DUSs), assessing the non-adherence of hospital physicians to the European Product Information for HES 130-containing medicinal products revised in 2014 [regarding indication, contraindications, and posology (dosage)], have shown in 2017 that the implemented restrictions for the use were not being sufficiently adhered to (ENCePP Register)[4]. Therefore, the concerned MAHs have been requested in 2018 to implement a set of further risk minimisation measures as outcome of the finalised Article 107i procedure of Directive 2001/83/EC for HES-containing medicinal products (EMEA/H/A-107i/1457) [implementing European Commission decision dated 17 Jul. 2018]. These safety measures are

- Dissemination of Direct Healthcare Professional Communication to inform about the DUSs results and the outcome of the Article 107i procedure,
- Adding a box warning not to use HES in patients with sepsis, renal impairment or in critically ill patients on top of the product information,
- Training of healthcare professionals on the appropriate HES usage,
- Implementation of a Controlled Access Programme to ensure that HES solutions are only delivered to accredited hospitals where healthcare professionals expected to prescribe/administer these medicinal products have been trained on their appropriate use.

Furthermore, the MAHs of HES solutions for infusion shall perform a DUS to assess the effectiveness of these risk minimisation measures. Therefore, this DUS will be conducted.

8 Research Question and Objectives

The primary objective of the DUS is to assess the non-adherence of physicians in HES-accredited hospitals to the approved European PIs [regarding indication for use and the contraindications and posology (dosage)] for HES 130-containing medicinal products in clinical routine after implementation of a set of risk minimisation measures. This allows to evaluate the effectiveness of these measures.

9 Research Methods

9.1 Study Design

The study is a retrospective, non-interventional, multinational, European DUS of use of HES 130-containing medicinal products of the concerned MAHs (Annex 1a/1b) in HES-accredited hospitals. The DUS will follow national laws and regulations.

Rationale: Inclusion of several study hospitals in several EU member states is intended to provide a reliable record of physicians' non-adherence to the HES PIs in the EU.
To obtain data from routine clinical use of HES 130 products, a non-interventional design is suitable, as all diagnostic and therapeutic measures are at the physician's discretion.

9.2 Setting

The setting is any HES-accredited hospital in the countries specified in Section 9.2.1 using HES 130 of Fresenius Kabi or B. Braun Melsungen (see Annex 1a/1b) and willing to document HES 130-treated patients.

9.2.1 Countries, Feasibility and Site Selection

Prior to the start of the DUS, a feasibility survey will be performed by the CRO. The feasibility check of HES-accredited hospitals intends to evaluate e.g.

- which wards of the hospitals have prescribed HES 130 products listed in Annex 1a/1b after HES accreditation
- whether patients had been treated with HES 130 within the documentation period (see Section 9.4)
- the number of patients which have been prescribed with HES 130 by physicians of these wards
- whether the wards at the HES-accredited hospitals have the qualified resources to be compliant with the procedures of case assessment, data entry, and verification mentioned in this study protocol (see Section 9.3 and Section 9.8.1)
- whether the HES-accredited hospitals used electronic patient data management system (PDMS) or paper-based documentation within the documentation period (see Section 9.4)
- whether the HES-accredited hospitals have a defined policy for collection of patient consent for using retrospective data for research projects
- whether the sites are willing to participate

Electronic PDMS allows a more convenient review of patient charts at the hospital regarding prescription of HES in the given retrospective data collection period compared to paper-based documentation. Hospitals which prescribed HES to a sufficient number of patients in the documentation period (see Section 9.4) will be preferred. The use of electronic PDMS will be considered secondary in the selection process and will not overrule the prescription frequency. Therefore, selection of hospitals with combined use of electronic PDMS and paper-based documentation or use of only paper-based documentation will be possible.
The CRO will discuss the results of the feasibility survey with the sponsor.

The DUS is intended to be conducted in a representative sample of member states of the EU, e.g. Belgium, Czech Republic, France, Germany, Hungary, Italy, Poland, Spain, The Netherlands. Final country selection will be based on the results of the feasibility, countries with high non-adherence rates participating in the first HES DUSs (ENCePP Register)[4], HES 130 sales figures and the willingness of HES-accredited hospitals to participate in this DUS.

9.2.2 Source Population

The source population includes all patients fulfilling the inclusion (see Section 9.2.3) and none of the exclusion criteria (see Section 9.2.4).

In the context of this DUS, the inclusion and exclusion criteria are minimised to obtain a representative overview of the routine use of HES 130 in clinical practice in HES-accredited hospitals in the EU.

Patient documentation at study site is planned in a consecutive order (for further details see Section 9.4).

9.2.3 Inclusion Criteria

- Patients who received any of the HES 130 solutions listed in Annex 1a/1b after implementation of a set of risk minimisation measures at the respective HES-accredited hospital in the documentation period (see Section 9.4)

Rationale: To assess the effectiveness of a set of risk minimisation measures, it is important that the patients are treated with HES 130 after the respective hospitals have been accredited for the use of HES.

9.2.4 Exclusion Criteria

- Patients who participated in interventional clinical trials investigating HES up to 3 months prior to or during the recorded HES infusions(s)

Rationale: Patients who were treated in an interventional clinical trial investigating HES are excluded, since a clinical trial protocol may require study specific use outside clinical routine practice.

9.3 Variables

Primary Variable

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 products (see Annex 1a/1b), the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology).

No specifications regarding diagnostic methods, medication or therapeutic procedures for the centres are pre-defined.

Variables to be Documented in the eCRF

A) Basic Information

An investigator or delegated trained study staff member is allowed to enter the following data into the eCRF:

- Hospital information [name, address, date (Day, Month, Year) of initial hospital accreditation, type of hospital (teaching/non-teaching, rural/urban, governmental/private)]
- Pseudonymised unique patient identifier
- Patient's hospital admission date (calendar week, year)
- Patient's discharge date (calendar week, year)
- Patient's demographics
    - Age (< 18 years or ≥ 18 years)
    - Weight

- Prehospital Field
    - Crystalloids used before admission to the study hospital? (yes/no)
    - HES 130 administered before admission to the study hospital? (yes/no)

      If yes,

        - Place/institution (ambulance vehicle, other)
        - Trade name of any prescribed HES product
        - HES 130 posology (dosage)

          Note: Infusion of > 30 mL/kg for 24 hours of HES 130 (6 %) and > 18 mL/kg of HES 130 (10 %) for 24 hours is considered as off-label use.

          Infusion of HES 130 for > 24 hours is considered as off-label use.

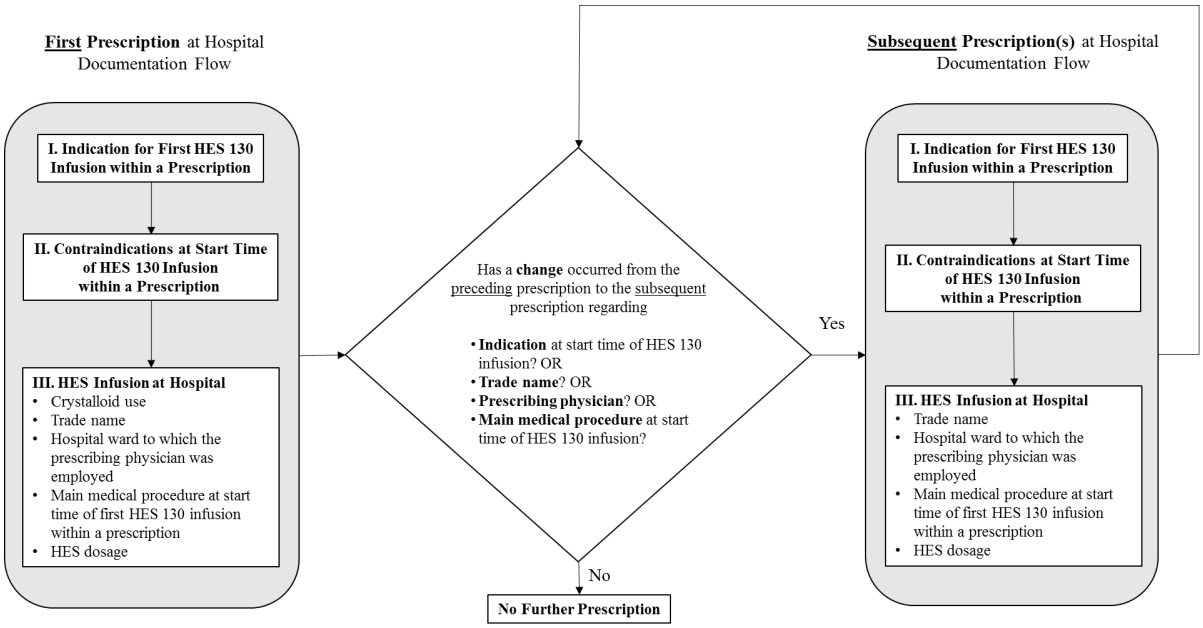
            - HES infusion (first to last bag/bottle)
                - Start of infusion (Day, Month, Year/Time hh:mm) of first bag/bottle
                - End of infusion (Day, Month, Year/Time hh:mm) of last bag/bottle
                - Total amount infused (from first to last bag/bottle) before admission to the study hospital (mL)

B) Prescriptions at Hospital
Documentation of the variables stipulated in I. to III. (see below) starts with the first prescription. It will be considered as a new (subsequent) prescription if a change of the following occurred

- Indication at start time of HES 130 infusion OR
- Trade name OR
- Prescribing physician OR
- Main medical procedure at start time of HES 130 infusion

The variables to be documented within the first or subsequent prescriptions are depicted in Figure 1 below.

Figure 1 Documentation Flow for Prescriptions



I. Indication for First HES 130 Infusion Within a Prescription

A specialised investigator (e.g. anaesthesiologist, emergency care physician) has to assess the case, and enter the data in the eCRF regarding indication. The specialised investigator must have been trained regarding the correct use of HES 130 by using the training material of the controlled access programme. For independent assessment this specialised investigator must not have had prescribed HES 130 for the treatment of the respective patient.

- The indication "Treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient" at the start time of first HES 130 infusion within a prescription applies? (yes/no/not possible to conclude due to retrospective design)

  Note 1: Acute blood loss can be usual and/or abnormal and/or unexpected bleeding

  Note 2: If the case is assessed as "not possible to conclude due to retrospective design" by the investigator, it is aimed to find a conclusion between the investigator and prescriber. If no final conclusion is reached, the assessment of the indication remains as "not possible to conclude due to retrospective design" and will not be classified as off-label use.

  Note 3: In case HES was applied although the indication was not fulfilled at the start time of HES infusion within a prescription, this is judged as off-label use

  If no, reason for HES 130 infusion [plain diagnosis text will be coded according to latest version of Medical Dictionary for Regulatory Activities (MedDRA)] has to be justified

  If "not possible to conclude due to retrospective design", has the prescriber been consulted by the investigator? (yes/no)

II. Contraindications Present at Start Time of HES Infusion Within a Prescription

A specialised investigator (e.g. anaesthesiologist, emergency care physician) has to assess the case, and enter the data in the eCRF regarding contraindications. The specialised investigator must have been trained regarding the correct use of HES 130 by using the training material of the controlled access programme. For independent assessment this specialised investigator must not have had prescribed HES 130 for the treatment of the respective patient.

Note 1: In the case that HES 130 product (see Annex 1a/1b) was applied although a contraindication was present and known at the start time of HES 130 infusion within a prescription, this is judged as off-label use.

Note 2: If information on contraindications is not available at the start time of HES infusion within a prescription, it cannot be judged as non-adherence; e.g. if serum creatinine data indicating renal impairment are not available at the time of HES 130 infusion is initiated, but only become available afterwards.

- Hypersensitivity to active substances or to any of the other excipients in the HES product? (yes/no)

  If yes, history of this hypersensitivity documented in the patient files (yes/no)

- Burns

  Note: Burns resolved and/or absent at start time of HES 130 infusion within a prescription are not to be considered as contraindication, e.g. burns in medical history. In addition, unknown pre-existing burns only becoming known or burns occurring/noticed after HES 130 infusion within a prescription are also not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Renal impairment or renal replacement therapy
    - Renal impairment

      Note: Renal impairment which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. renal impairment in medical history. In addition, unknown pre-existing renal impairment only becoming known or renal impairment occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

      Renal impairment definition is provided in Annex 2.

      Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

    - Renal replacement therapy (RRT)

      Note: Patient not under acute RRT at start time of HES 130 infusion within a prescription is not to be considered as contraindicated patient, e.g acute RRT in medical history or initiated after HES 130 infusion.

      Furthermore, permanently terminated chronic RRT in medical history or chronic RRT initiated after HES 130 infusion is not to be considered as contraindication.

      Renal replacement therapy definition is provided in Annex 2.

      Patient under acute RRT at start time of HES 130 infusion within a prescription? (yes/no)

      Patient under permanent chronic RRT at start time of HES 130 infusion within a prescription? (yes/no)

- Intracranial or cerebral haemorrhage

  Note: Intracranial or cerebral haemorrhage which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. intracranial or cerebral haemorrhage in medical history. In addition, unknown pre-existing intracranial or cerebral haemorrhage only becoming known or intracranial or cerebral haemorrhage occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Critically ill patient [typically admitted to the intensive care unit (ICU)]

  Note: Critical illness which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. critical illness in medical history. In addition, unknown pre-existing critical illness only becoming known or critical illness occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  If the patient was under special surveillance/monitoring (e.g. in a post-operative situation), but was not critically ill, this is not to be considered as a contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

  If yes, reason why considered critically ill:

  - Sepsis (yes/no)

  Note: Sepsis which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. sepsis in medical history. In addition, unknown pre-existing sepsis only becoming known or sepsis occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Sepsis definition is provided in Annex 2.

  - Other reason why considered critically ill (yes/no)

    If yes, plain diagnosis text will be coded according to latest version of MedDRA

- Hyperhydration

  Note: Hyperhydration which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. hyperhydration in medical history. In addition, unknown pre-existing hyperhydration only becoming known or hyperhydration occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Pulmonary oedema

  Note: Pulmonary oedema which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. pulmonary oedema in medical history. In addition, unknown pre-existing pulmonary oedema only becoming known or pulmonary oedema occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Dehydration

  Note: Dehydration which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. dehydration in medical history. In addition, unknown pre-existing dehydration only becoming known or dehydration occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Hypovolemia/need for fluid resuscitation without extra-/intracellular dehydration is not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Severe hyperkalaemia (only in case of potassium-containing HES solutions)

  Note: Severe hyperkalaemia which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. severe hyperkalaemia in medical history. In addition, unknown pre-existing severe hyperkalaemia only becoming known or severe hyperkalaemia occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Severe hyperkalaemia definition is provided in Annex 2.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Severe hypernatraemia

  Note: Severe hypernatraemia which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. severe hypernatraemia in medical history. In addition, unknown pre-existing severe hypernatraemia only becoming known or severe hypernatraemia occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Severe hypernatraemia definition is provided in Annex 2.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Severe hyperchloraemia

  Note: Severe hyperchloraemia which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. severe hyperchloraemia in medical history. In addition, unknown pre-existing severe hyperchloraemia only becoming known or severe hyperchloraemia occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Severe hyperchloraemia definition is provided in Annex 2.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Severely impaired hepatic function

  Note: Severely impaired hepatic function which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. severely impaired hepatic function in medical history. In addition, unknown pre-existing severely impaired hepatic function only becoming known or severely impaired hepatic function occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Severely impaired hepatic function definition is provided in Annex 2.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Congestive heart failure

  Note: Congestive heart failure which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. congestive heart failure in medical history. In addition, unknown pre-existing congestive heart failure only becoming known or congestive heart failure occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Severe coagulopathy

  Note: Severe coagulopathy which has been corrected and was thus absent at start time of HES 130 infusion within a prescription is not to be considered as contraindication, e.g. severe coagulopathy in medical history. In addition, unknown pre-existing severe coagulopathy only becoming known or severe coagulopathy occurring/noticed after HES 130 infusion is also not to be considered as contraindication.

  Severe coagulopathy definition is provided in Annex 2.

  Present and known at the start time of HES 130 infusion within a prescription? (yes/no)

- Organ transplant patient? (yes/no)

  Note: HES 130 treatment of organ transplanted patients or patients in/for an organ transplantation procedure is to be considered as contraindication

- In case any of the contraindications applied at the start time of HES 130 infusion within a prescription, reason for HES infusion despite these contraindications (plain diagnosis text will be coded according to latest version of MedDRA) has to be justified.

III. HES Infusions

An investigator or delegated trained study staff member is allowed to enter the data for the following items into the eCRF:

- Crystalloids used
  - prior to <u>first</u> HES 130 prescription? (yes/no)

    Note: If crystalloids were used in the prehospital field (e.g. ambulance vehicle) prior to the first HES 130 prescription at the hospital, "yes" has to be selected.
  - concomitantly to first HES 130 prescription? (yes/no)

- Trade name of any prescribed HES 130 product

- Hospital ward in which the HES 130-prescribing physician was employed
    - Trauma/Emergency
    - Anaesthetics/Pain Management
    - Burn Centre/Unit
    - Cardiology
    - Gastroenterology
    - Intensive/Critical Care Unit
    - Neurology
    - Obstetrics/Gynaecology/Maternity
    - Orthopaedics
    - Paediatrics
    - Surgery
    - Urology
    - Other, please specify

- Main medical procedure the patient underwent (e.g. hip replacement, knee replacement, abdominal aortic surgery, treatment of traumatic injuries) at start time of first HES 130 infusion within a prescription (plain medical procedure text will be coded according to latest version of MedDRA)

- HES 130 dosage (posology)

  Note: Infusion of > 30 ml/kg for 24 hours of HES 130 (6 %) and > 18 ml/kg of HES 130 (10 %) for 24 hours is considered as off-label use. Infusion of HES 130 for > 24 hours is considered as off-label use.

    - HES infusion (first to last bag/bottle)
        - Start of infusion (Day, Month, Year/Time hh:mm) of each bag/bottle
        - Amount infused (ml) of each bag/bottle
        - End of infusion (Day, Month, Year /Time hh:mm) of each bag/bottle

9.4 Data Sources

Data will be collected retrospectively from charts of patients treated previously with HES 130. Data entry based on patient charts will be performed by investigator and/or delegated qualified study staff at the participating HES-accredited hospital using the eCRF (for more details refer to Section 9.3).

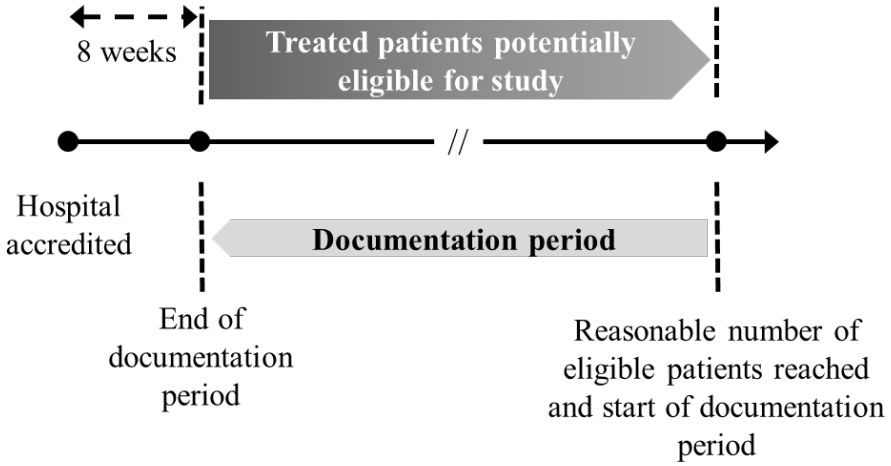
The documentation process is defined as follows (see Figure 2):

- After accreditation of the hospital and once a reasonable number[$] of patients has been treated with HES 130 documentation period begins with the most recently treated eligible patient at the respective HES-accredited hospital.
- Further eligible patients will be documented chronologically backwards week by week until 8 weeks after initial accreditation of the hospital
- The order of patient documentation will be determined by the date of initial HES 130 infusion
- Overall study documentation will be stopped once the targeted number of patients for the study (see Section 9.5) is reached

All data will be pseudonymised.

[$] This will depend on the results of the feasibility survey.

Figure 2 Documentation Process



Note: Patients treated with HES 130 within the documentation period, but admitted to the hospital before the end of documentation period (i.e. within the 8-week period after hospital accreditation), are allowed to be documented. Documentation of data from patients treated with HES 130 before the end of the documentation period (within the 8-week period after accreditation of hospital) will not be allowed.

9.5 Study Size

The sample size calculation is based on the primary statistical unit of the study: Patients treated with HES 130.

For potential non-adherence rates of 5 % to 95 % and aiming for a precision (defined as the confidence interval width) of up to 5 percent points of the exact two-sided 95 % confidence interval (according to Clopper-Pearson) for the evaluation of non-adherence, a sample size of 1574 patients is required. To compensate for potential cases where the indication for use has been assessed as “not possible to conclude due to retrospective design” or missing data regarding posology (assumption of 10 %), 1749 patients will be documented.

In case the intended targeted sample size of 1749 could not be reached in the documentation period, analysis with a sample size of 1220 (including 10 % compensation for cases assessed as “not possible to conclude due to retrospective design” or missing data regarding posology) will be performed to ensure a precision (confidence interval width) of at least 6 percent points.

However, the sponsor will make any effort to reach the intended target sample size of 1749.

9.6 Data Management

9.6.1 Database

Data entered in the eCRF will be stored centrally in a database, which is maintained according to current standards for hard- and software (21CFR11 compliance, i.e. includes an audit trail) security, including daily backups and access to the data files only for investigators and/or qualified study staff involved in the DUS. The sponsor will only have access to pseudonymised data. For the HES-accredited DUS study sites, the CRO will assign a secure login for investigators and/or qualified study staff, who will be responsible for documentation. Access for respective staff members will be granted depending on their roles and tasks, and documented in the site delegation log. The secure login allows the investigators and/or qualified study staff to enter the data into the eCRF.

9.6.2 Patient Data Pseudonymisation

Patient data investigated (variables specified in Section 9.3) will be pseudonymised (a unique identifier) to secure the confidentiality of the patients' data. This will allow for any subsequent enquiries in relation to possible incomplete or inconclusive data to be resolved by the participating hospital.

Only pseudonymised data will be passed to the sponsor or published if applicable. The sponsor will not be able to backtrack to the identification of the patient.

The participating hospital staff will keep the coding/encryption key for the pseudonyms so that it is still possible for them to identify the individual patients, if required. Coding/encryption keys to identify patients will be kept separate from the rest of the data files, all of which will be maintained in password-protected servers and/or locked file cabinets. Hence, the codes/encryption keys will be accessible for investigators and/or qualified study staff only and if applicable for inspections by authorities. Keeping the codes during the conduct of the study will allow for clarification of data discrepancies.

For data protection reasons, onsite monitoring is not possible in this study, i.e. no personnel other than hospital staff will have access to patient records. Instead, data entry should be conducted by applying the four-eyes principle i.e. source data verification will be performed by two persons on indication and contraindications (Section 9.8.1). In case of unresolved discrepancies, the final decision will be taken by the local principal investigator at the respective study site.

After endorsement of the final study report by EMA/PRAC, the codes to identify patients will be destroyed by the investigator.

9.7 Data Analysis

9.7.1 Methods

Due to the exploratory character of this study only descriptive statistics will be used for the analysis of the variables listed in Section 9.3. For continuous variables, mean ± standard deviation, median and quartile (25^{th}; 75^{th} percentile) and numbers of non-missing and missing values will be presented. For categorical variables, frequencies and percentage will be shown for each category and for missing values.

Primary Variable

To assess the non-adherence of hospital physicians to the approved European PIs of HES 130 solutions (see Annex 1a/1b), the primary variable will be the number and proportion of patients whose treatment during the hospital stay did not adhere to the approved European PIs regarding indication, contraindications and dosage (posology)**. The full analysis set will comprise all eligible patients.

The number and percentage of patients who received HES 130 and were documented as non-adherent to one or more of the specifications made in the PIs (concerning the indication, contraindications and dosage) will be evaluated for the overall patient population and will be displayed together with 95 % confidence intervals for the percentage.

For the primary analysis, missing data regarding indication and posology (dosage) will neither be defined as non-adherent nor adherent prescription; this also applies if "not possible to conclude due to retrospective design" is assessed regarding indication. If more than one HES 130 prescription is reported for the same patient, every single prescription needs to adhere to the approved European PIs for counting the patient's total HES 130 treatment as adherent. That means, if at least one prescription will be non-adherent, the patient's total HES 130 treatment will be counted as non-adherent (see also Figure 3 and Figure 4 below).

Sensitivity Analyses of the Primary Variable

In addition, sensitivity analyses of the primary variable will be conducted in which "not possible to conclude due to retrospective design" regarding indication will be evaluated as

- non-adherent prescription (sensitivity analysis 1)
- adherent prescription (sensitivity analysis 2)

** Infusion of HES 130 for > 24 hours is considered as off-label use. Infusion of > 30 ml/kg for 24 hours of HES 130 (6 %) and > 18 ml/kg of HES 130 (10 %) for 24 hours is considered as off-label use.

Furthermore, sensitivity analyses regarding the contraindications of special interest (critically ill, sepsis, renal impairment)[#] will be done. For these, missing values will be evaluated as

- non-adherent prescription (sensitivity analysis 3)
- adherent prescription (sensitivity analysis 4)

Further Analyses

Similar to the analysis of the primary variable, non-adherence to individual specifications made in the PIs will be evaluated (i.e. HES 130 use outside indication, presence of any contraindication at the start time of HES 130 infusion, presence of contraindications at the start time of HES 130 infusion by each type of contraindication and dosage outside the specifications made in the PIs).

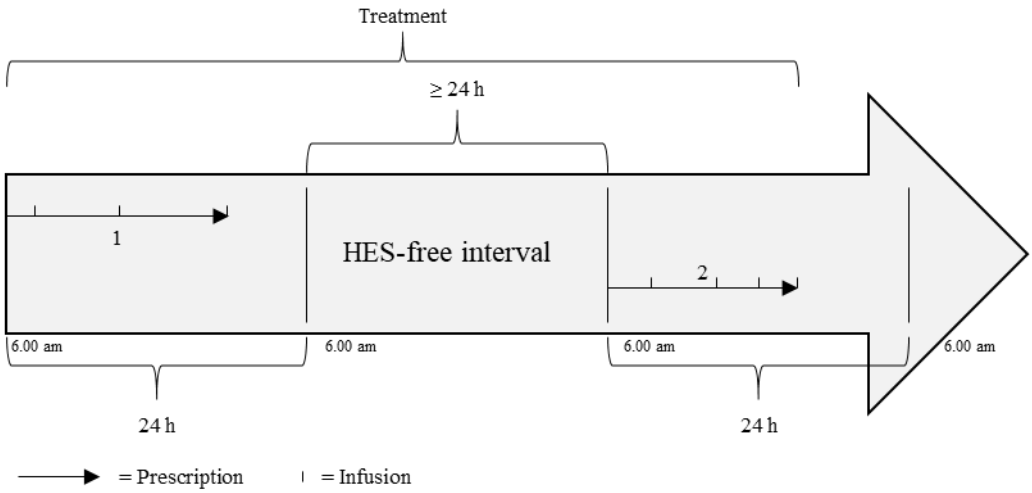
Additionally, the number and percentage of patients whose treatment during the hospital stay does not adhere to one or more specifications made in the approved European PIs [concerning the indication, contraindications and dosage (posology)] will also be evaluated for each country.

Furthermore, analysis of non-adherence to one or more specifications made in the approved European PIs (concerning the indication, contraindications and dosage [posology]) will also be conducted for each single HES 130 prescription as statistical unit for assessment (instead of considering the patient as statistical unit) and will be presented as secondary measure.
For this purpose, each prescription is defined as a treatment with a single or multiple HES 130 infusion(s) in a row until a change of the following occurred (see also Figure 1 above):

- Indication at start time of HES 130 infusion OR
- Trade name OR
- Prescribing physician OR
- Main medical procedure at start time of HES 130 infusion OR
- The subsequent HES 130 infusion was interrupted from the previous HES 130 infusion by a HES-free interval of ≥ 24 h (see example in Figure 3). To minimise calculation errors by the sites this definition will be applied technically (and is therefore not defined in Section 9.3, Figure 1).

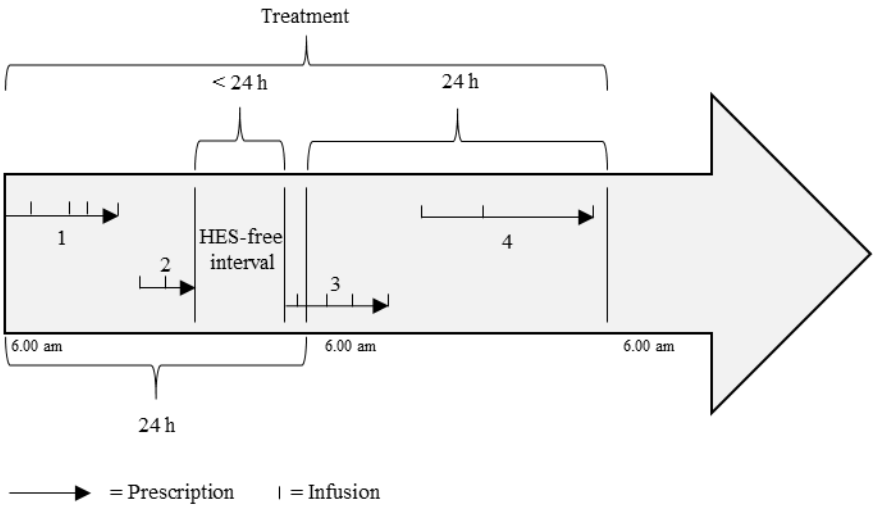
[#] Main focus of PRAC

Figure 3 Example A for Prescription



In case the treatment duration (including HES-free interval(s) of < 24 h) exceeded 24 h and comprised several single prescriptions as defined above, only prescriptions exceeding the 24 h period will be regarded as non-adherent (see example in Figure 4 prescriptions 3 and 4).

Figure 4 Example B for Prescription



Analyses of non-adherence according to (i) hospital type, and (ii) patients' age category will be conducted on patient level as primary statistical unit of the study as well as on prescription level. Additionally, analysis of non-adherence according to hospital wards will be performed on prescription level.

Furthermore, the medical procedures will be evaluated; details will be described in the statistical analysis plan.

Mean cumulative and mean maximum daily dose will be calculated for analysis of exposure to HES products for the overall patient population.

Missing/implausible data in the eCRF will be detected via automatic edit checks by the electronic data capture (EDC) system, during data entry. Implausible data can be detected automatically and/or manually and prompted to be corrected. Missing/implausible data will be followed up by the CRO data management with the investigator. Data that remain missing will not be imputed.

Further details of the analysis will be described in a statistical analysis plan which will be finalised prior to database closure.

9.7.2 Validity of Outcome Measures

Assessing non-adherence of hospital physicians to the PI specifications in a non-interventional and retrospective DUS can reduce potential bias. However, this DUS has potential limitations (see Section 9.9).

The aim to include several HES-accredited hospitals of several European countries and the intended consecutive inclusion of patients should provide a meaningful record of HES 130-containing medicinal products used in routine clinical practice.

9.8 Quality Control

The generation of the study protocol is based on the "Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies" (EMA 2012)[5].

Moreover, Sponsor's and/or CRO's standard operation procedures (SOPs) are used for planning, conducting, reporting and archiving of the study. Quality measures are defined in these SOPs.

9.8.1 Procedures in the Participating Hospital

Each hospital designates one principal investigator (who will be supported by the appointed CRO). The principal investigator will be responsible for:

- Obtaining local Independent Ethics Committee (IEC) approval (if required by local requirements) for the conduct of the DUS in his/her HES-accredited hospital
- Obtaining a waiver for signed written patient data protection consent if required according to HES-accredited hospital/national policy

- Assigning site staff and ensuring that the assigned staff is properly trained (e.g. for the study protocol and eCRFs)
- Ascertainment of data accuracy, i.e. he/she is responsible for a complete and correct recording of data in the eCRFs in the respective HES-accredited hospital (he/she should apply the four-eyes principle) to assure high quality of data. Therefore, source data verification on data entered by a specialised investigator regarding indication and contraindication (in eCRF) should be performed by trained study staff member (e.g. study nurse). Application of four-eyes principle could be documented in the eCRF. In case of unresolvable discrepancies, i.e. no conclusion could be reached between both persons regarding indication and contraindication, the final decision will be taken by the local principal investigator at the respective site
- Ensuring that only qualified study staff members conduct the following:
    - A specialised investigator (e.g. anaesthesiologist, emergency care physician; see Section 9.3) has to assess the cases, enter data, and verify the data regarding indication and contraindications in the eCRF (this also applies if changes regarding indication/ contraindications occur)
    - Investigators or delegated trained study staff members are allowed to enter data on Basic Information, posology (dosage), HES 130 trade name, hospital ward, main medical procedure, crystalloid use
- Notification to the CRO, in advance of documentation and at any time after start of documentation, if the retrospective recording is not or no longer possible or feasible (e.g. due to changes in the resource situation in the participating HES-accredited hospital).

Depending on national and local requirements, the CRO will facilitate tasks for the principal investigator, e.g. by compiling documents for submission/notification to the IEC and obtaining positive opinion, if necessary. Furthermore, the CRO will provide training material and will raise queries to the investigator regarding missing or inconclusive data recorded in the eCRF.

Each participating HES-accredited hospital will receive an Investigator Site File from the CRO prior to the start of the DUS, containing at least the following documents:

- DUS study protocol
- Manual for eCRF
- Documents of IEC
- Training slides for investigators and delegated qualified study staff
- CRO's and Sponsor's contact details

In addition to the programmed edit, logic and manual checks of the EDC system (see Section 9.8.2), source data verification on data entered by a specialised investigator regarding indication and contraindication in the eCRF should be performed by applying the four-eyes principle as defined above.

9.8.2 Procedures at the Contract Research Organisation (CRO) to Ensure Reliable Data Quality

Edit and logic checks will be specified in a data validation plan and will be programmed into the EDC system to ensure high-quality data. Missing/implausible data will be highlighted to the investigators and/or qualified study staff member at the participating hospitals and will be prompted to be corrected/completed. All requests to complete missing data fields in the eCRF will be shown during data entry to the sites by the EDC system, so that sites can readily access individual patient data to complete data if necessary.

As a quality assurance measure it is intended to perform a pre-testing including a medical review prior to conduct of the study in which the eCRF will be assessed to identify potential issues such as misunderstanding provided that sufficient time is granted. This will also help to reduce potential amendments during documentation of the study. After the "go live" of the EDC system, data management activities will include data review for consistency.

Qualified English speaking personnel at the CRO will be available during all regular working hours (9 am – 5 pm) to answer any immediate technical or procedural questions by the investigators or qualified staff members from the centres.

All data will be prepared, pseudonymised and stored in data formats that are suitable for external auditing and inspection at any time the need should arise.

The CRO is responsible for e.g. performing eCRF training and providing all relevant documentation to the investigator at each centre as specified in Section 9.8.1.

The CRO will assign a secure login for investigators and/or qualified study staff who will be responsible for documentation. The secure login allows the investigators and/or qualified study staff to enter the data into the eCRF. The CRO will track assigned and withdrawn secure logins to the eCRF.

9.9 Limitations of the Research Methods

The following types of bias or limitations may occur in this retrospective, non-interventional DUS:

- Prescription behaviour of physicians might be influenced by the preceding feasibility survey
- Number of HES-accredited sites/hospitals and physicians willing to participate in the conduct of this DUS might be limited, i.e. the number of participating sites/hospitals might be not representative, and the intended sample size might not be reached in the documentation period
- Incomplete/implausible data in the individual patients' original medical records may not be possible to be clarified and/or remain not assessable
- Due to retrospective design determination of indication (e.g. acute blood loss) and contraindications (e.g. dehydration) might not be clearly possible based on patients' charts of already treated patients. Such cases will remain not assessable
- For contraindications such as severe hypernatraemia, severe coagulopathy, and severely impaired hepatic function mentioned in the EU HES PIs there are no generally accepted/established definitions which are uniformly used by different hospitals or physicians. Evaluation of contraindications based on post-hoc definitions in the context of a retrospective DUS will not necessarily match current local guidelines and the patient assessment of the prescribing physician at the time of patient treatment (e.g. a prescribing physician assessed the patient as having no severely impaired coagulation, while the post-hoc definition provided in Annex 2 categorises the patient as having severe coagulopathy, i.e. false-positive non-adherence)
- Source data verification of the data by the CRO/sponsor by reviewing the individual patients' original medical records will not be possible. However, data entered in the eCRF regarding indication and contraindication should be verified by applying the four-eyes principle (Section 9.8.1)

9.10 Other Aspects

Not applicable.

10 Protection of Human Subjects

This DUS is a retrospective, non-interventional study documenting data from clinical routine. Thus, this retrospective study:

- does not pose any risk to study subjects,
- is conducted in the interest of the public's health,
- will apply data protection and pseudonymisation measures to ensure confidentiality according to local legal requirements

The DUS will be conducted in accordance with the study protocol, the Declaration of Helsinki (2013)[6], and any applicable local regulations. Special attention will be paid to data protection laws, adhering to EU General Data Protection Regulation (2016)[7].

To safeguard confidentiality of direct patient related data, no personal identifiers will be provided to the sponsor. Depending on national law and local regulations the DUS study protocol will be submitted to the responsible IEC to receive their opinion and to request to waive informed consent according to the International Society for Pharmacoepidemiology (ISPE) guideline on data privacy standard, Section IV[8], because obtaining retrospectively informed consent of several hundred patients to use data from charts review for research purposes is considered not feasible. If waiving informed consent is not possible, the respective HES-accredited hospital for which waiving is not possible will therefore not be selected.

It must be ensured that eCRFs or any other documents transmitted to the sponsor do not contain names, but only pseudonymised unique identifiers.

Only the investigator and/or delegated qualified study staff at the participating centre will have the means to identify a patient's name/other personal details via the unique identifier.

10.1 Independent Ethics Committees (IECs)

If necessary and according to applicable regulations, the sponsor, the appointed CRO, or the responsible site in the HES-accredited hospital/the principal investigator will:

- Notify or obtain opinion from the relevant IEC regarding the study protocol, and any amendments, Request to waive informed consent according to the ISPE guideline on data privacy standard, Section IV (see Section 10 of this DUS study protocol).
- Submit periodic updates on the progress of the study to the relevant IEC,
- Notify the relevant IEC of the end-of-study,
- Submit a summary of the study results to the relevant IEC, i.e. an abstract of the final DUS study report.

The CRO will keep an updated list of all submission and approval dates of all documents submitted to the IECs.

10.2 Competent Authorities

The study protocol and substantial amendments will be submitted to the PRAC of EMA for approval prior to implementation.

If required according to local regulations, the national competent authority and/or other national or regional authorities will be notified about the DUS and provided with the required documents for approval.

Progress on the ongoing DUS will be reported within the upcoming Periodic Safety Update Report (PSUR).

11 Management and Reporting of Adverse Events/Adverse Reactions

This study will retrospectively use patient charts as data source, i.e. secondary use of data. Furthermore, the identification of suspected Adverse Drug Reactions (ADR) is not the objective of this DUS; instead the physician's non-adherence to the approved European PIs for HES 130-containing products (Annex 1a/1b) will be assessed. Therefore, documentation of ADRs is not intended. This will also ensure that ADRs already reported by the physicians in the past will not be counted twice.

12 Plans for Disseminating and Communicating Study Results

The appointed CRO will prepare the study report based on the results obtained. It will be prepared according to the specification stated in the EMA Guideline on GVP – Module VIII section VIII B.4.3.2 (EMA 2017)[9], as well as the "Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies" (EMA 2013)[10].

The final study report will be provided to EMA´s PRAC. The participating sites will be informed about the results when the report is finalised.

Key results of the study are intended to be published in the publicly available EU PAS register (The European Union electronic Register of Post-Authorisation Studies)[11].

13 References

1 Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. N Engl J Med 2012; 367(2):124-34.

2 Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012; 367(20):1901-11.

and Supplement to: Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012. DOI: 10.1056/NEJMoa1209759.

3 Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008; 358(2):125-39.

4 ENCePP Register no. EUPAS10897 (Retrospective Drug Utilisation Study by Fresenius Kabi to investigate the routine use of Hydroxyethyl Starch (HES)- containing Infusion Solutions in Hospital) and EUPAS12540 (Retrospective Drug Utilisation Study to investigate the routine use of Hydroxyethyl Starch (HES)-containing Infusion Solutions of B. Braun Melsungen AG in Hospitals).

5 European Medicines Agency. Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, Patient Health Protection, EMA/623947/2012, 26 Sep. 2012.

6 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013; 310(20):2191-4.

7 Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 Apr. 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). Date of document: 27 Apr. 2016. Official Journal of the European Union 4 May 2016; L119.

8 ISPE Position Paper “Data Privacy, Medical Record Confidentiality, and Research in the Interest of Public Health”, 1997, amended 1998.

Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at the given weblink (accessed 21 Sep. 2018):

www.pharmacoepi.org/resources/policies/privacy/

9 European Medicines Agency. Guideline on good pharmacovigilance practices (GVP), Module VIII – Post-authorisation safety studies (Rev 3). EMA/813938/2011 Rev 3. 9 Oct. 2017.

10 European Medicines Agency. Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies, 30 Jul. 2013, EMA/48663/2013.

11 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The European Union electronic Register of Post-Authorisation Studies (EU PAS Register), www.encepp.eu/encepp/studiesDatabase.jsp.

Annex 1. List of Stand-Alone Documents

Number	Document Reference Number	Date	Title
Annex 1a	Annex 1a, Version 2.0		List of HES 130-containing medicinal products registered in those countries in which DUS is planned to be performed (Fresenius Kabi Deutschland GmbH)
Annex 1b	Annex 1b, Version 2.0		List of HES 130-containing medicinal products registered in those countries in which DUS is planned to be performed (B. Braun Melsungen AG)
Annex 1c	Annex 1c, Version X.X		HES DUS participating investigator and hospital list

Annex 2. Definitions of Specific Contraindications in this DUS

Annex 3. ENCePP Checklist for Study Protocols

Annex 4. Signature Page(s)