Study Protocol for Drug Utilisation Study for Hydroxyethyl Starch (HES) Solutions

PASS Information

Title	Retrospective Drug Utilisation Study to investigate the routine use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in Hospitals
Protocol Version Identifier	HES DUS Protocol_Version 1.4_07 May 2015
Date of Last Version of Protocol	07 May 2015
EU PAS Register Number	*Will be submitted after finalisation of protocol and approval by the PRAC*
Active Substances	**Fresenius Kabi Deutschland GmbH:** Poly(O-2-hydroxyethyl)starch Sodium chloride Sodium acetate trihydrate (for Volulyte) Potassium chloride (for Volulyte) Magnesium chloride hexahydrate (for Volulyte) **ATC code:** Blood substitutes and plasma protein fractions B05AA07 hydroxyethylstarch

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.
Product Reference	Not applicable
Procedure Numbers	**Fresenius Kabi Deutschland GmbH:** DE/H/223/01; DE/H/1568/001/DC; DE/H/0619/01/DC; DE/H/295/01
Marketing Authorisation Holder(s)	**Fresenius Kabi Deutschland GmbH** Else-Kröner-Strasse 1 61352 Bad Homburg v.d.H. Germany Note: The registered marketing authorisation holder for the individual products in the European countries in which the DUS will be conducted is provided in Annex 1a.

Joint PASS	No
Research Question and Objectives	The objective of the Drug Utilisation Study (DUS) is to assess the adherence of hospital physicians to the revised European Product Information (PI) [Summary of Product Characteristics (SmPC); Package Leaflet] for Hydroxyethyl Starch (HES) - containing medicinal products concerning indication, posology (dosage) and contraindications (as listed in Annex III of the EC decision).
Country(-ies) of Study	Intended countries for conduct of DUS: Belgium, Czech Republic, France, Germany, Netherlands, Poland, Spain, Sweden, United Kingdom
Author	**Fresenius Kabi** Main author: [redacted]

Marketing Authorisation Holders

Marketing Authorisation Holder(s)	Fresenius Kabi Deutschland GmbH Else-Kröner-Straße1 61352 Bad Homburg v.d.H. Germany
MAHs Contact Person	[redacted]

1. Table of Contents

2. List of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
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
eCRF	Electronic Case Report Form
EC	European Commission
e.g.	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
EU-QPPV	European Union - Qualified Person Responsible For Pharmacovigilance
GVP	Good Pharmacovigilance Practice
GPP	Good Pharmacoepidemiology Practice
HES	Hydroxyethyl Starch
ICD-10	International Classification of Disease, tenth revision
i.e.	Id est, that is
IEC	Independent Ethics Committee
ICU	Intensive Care Unit
ISPE	International Society of Pharmaceutical Engineering
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCA	National Competent Authorities
NYHA	New York Heart Association
PASS	Post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
PDMS	Patient Data Management System
PI	Product Information
PICU	Paediatric Intensive Care Unit
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics
SAP	Statistical Analysis Plan

3. Responsible Parties

This Drug Utilisation Study (DUS) will be conducted by Fresenius Kabi Deutschland GmbH, Else-Kröner-Straße 1, 61352 Bad Homburg v.d.H. (Germany), as concerned marketing authorisation holder (MAH).

Contact persons for Fresenius Kabi Deutschland GmbH:

[redacted]

For this DUS, HES products of Fresenius Kabi, registered in those countries in which the DUS is performed, will be included. Fresenius Kabi as responsible MAH will monitor the progress of the DUS and receive status reports from the CRO concerning the number of documented patients. Due to the non-interventional and the retrospective design of the DUS, Fresenius Kabi will not have any influence on the treatment of the patients.

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

CRO contact details: [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 local law, a **coordinating investigator** in participating countries will be additionally assigned. Contact details and a list of all investigators and participating sites will be kept in a stand-alone document (see Annex 1b).

4. Abstract

Title
Retrospective Drug Utilisation Study to investigate the routine use of Hydroxyethyl Starch (HES)-containing Infusion Solutions in Hospitals

Protocol Version
Version 1.4, 07 May 2015

Date of the Protocol
07 May 2015

Main Author
[redacted]

Rationale and Background
The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recommended in the Article 107i procedure according to Directive 2001/83/EC for HES-containing medicinal products (EMEA/H/A-107i/1376) in October 2013 that HES solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality while the benefit-risk ratio for HES-containing medicinal products remains favourable in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.

The final implementing decision, issued by the European Commission (EC) on December 19, 2013, implicates new contraindications, new special warnings and precautions for use as well as other changes to the European Product Information (PI) [Summary of Product Characteristics (SmPCs); Package Leaflet] for risk minimisation measures (as requested in Annex III of this EC decision).

To "evaluate the effectiveness of the risk minimisation measures taken" (as requested in Annex IV of the EC decision), the concerned MAHs of HES products subject to the PRAC procedure were asked to conduct a Drug Utilisation Study (DUS) with HES-containing medicinal products in several European Union (EU) Member States.

Research Question and Objectives
The objective of the DUS is to assess the adherence of hospital physicians to the revised European PI for HES-containing medicinal products concerning indication, posology (dosage) and contraindications (as listed in Annex III of the EC decision).

Study Design
Retrospective, non-interventional, multinational, multi-centre DUS

Population
Patients treated with HES-containing infusion solutions in hospitals in the intended 9 European countries.

Variables
The DUS will document patient data describing the medical status at initiation of treatment, posology (dosage) and contraindications of HES to identify deviations from the revised European PI (as listed in Annex III of the EC decision).

Data Sources
Data will be collected retrospectively from patients previously treated with HES within a defined timeframe using patient charts. Primarily, study sites that are using an electronic Patient Data Management System (PDMS) for patient data documentation will be chosen. Data will be entered into secure online electronic case report forms (eCRFs) by investigators or delegated responsible persons based on patient charts. All data will be fully anonymised.

Study Size
In order to achieve sufficient precision of country-specific estimates of non-compliance to the revised European PI at least 334 patients per country are required. For nine countries, at least 3000 HES treated patients in total will be documented in the study.

Data Analysis
Descriptive analysis will be performed on data collected and will include absolute numbers and proportion of adherence to the revised European PI for the overall population and subgroups. 95 % confidence intervals on proportions of adherence will be provided.

Milestones
Start of retrospective data collection, i.e. "Date from which the data extraction from patient charts starts" – about 3 to 4 months after protocol approval by the PRAC and notification to national competent authorities (NCA) and positive Independent Ethics Committees (IEC) opinion as required by national and local regulations and requirements.

End of retrospective data collection, i.e. "Date from which the analytical data set is completely available" – about 9 to 12 months after start of data collection.

Final report of study results – will be submitted within 24 months of the final protocol approval by the PRAC.

5. Amendments and Updates

None

Number	Date	Section of study protocol	Amendment or update	Reason

6. Milestones

Milestone	Planned date
Start of data collection[a]	About 3 to 4 months after protocol approval by the PRAC and notification to NCAs and positive IEC opinion as required by national and local regulations and requirements.
End of data collection[b]	About 9 to 12 months after start of data collection.
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 protocol approval by the PRAC and before the start of data collection.
Final report of study results	Will be submitted within 24 months of the final protocol approval by the PRAC.

[a] Date from which the data extraction from patient charts starts
[b] Date from which the analytical data set is completely available

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, initiated procedures to assess the benefits and risks of HES-containing solutions, especially in critically ill patients.
In the relevant European referral procedure according to Article 107i of Directive 2001/83/EC for HES-containing medicinal product (EMEA/H/A-107i/1376) the PRAC, recommended in October 2013 that HES-solutions must no longer be used to treat patients with sepsis or burn injuries or critically ill patients because of an increased risk of kidney injury and mortality in these patients but that the benefit-risk ratio for HES-containing

medicinal products remains favourable in the treatment of hypovolaemia due to acute blood loss when crystalloids alone are not considered sufficient.
This recommendation was adopted by majority vote by the Coordination Group for Mutual Recognition and Decentralised Procedures human (CMDh). The final implementing decision was issued by the EC on December 19, 2013 by which this referral procedure was positively concluded. This implicates new contraindications, special warnings and precautions for use as well as other changes to the European PI for risk minimisation measures (as requested in Annex III of the EC decision).

In addition, the concerned MAHs were requested to conduct a DUS with HES-containing medicinal products in several EU Member States to "evaluate the effectiveness of the risk minimisation measures taken" (as requested in Annex IV of the EC decision).

The DUS will be performed by the MAH Fresenius Kabi Deutschland GmbH and will include all available HES-containing medicinal products of this MAH in those European countries where the DUS will be performed. A detailed overview about the concerned medicinal products in the individual country is provided in Annex 1a.

In summary, the scope of this DUS is to investigate the adherence of hospital physicians to the revised European PI for HES-containing medicinal products during routine administration of HES-solutions in hospitals to evaluate the effectiveness of the risk minimisation measures taken.

8. Research Question and Objectives

The objective of the DUS is to assess the adherence of hospital physicians to the revised European PI for HES-containing medicinal products concerning indication, posology (dosage), and contraindications (as listed in Annex III of the EC decision).

In general, due to its retrospective and non-interventional nature the DUS can only be used to generate hypotheses and not to test any a-priori specified hypothesis.

9. Research Methods

9.1 Study Design

The study is a retrospective, non-interventional, multinational, multi-centre European DUS of use of HES-containing medicinal products in hospitals. The DUS will follow national laws and regulations.

Outcome measure is the adherence to the concerned sections of the revised European PI for HES-containing medicinal products.
Usage of these medicinal products according to indications, posology (dosage), and contraindications as specified in the revised PI of the HES solutions will be assessed.

In the DUS, routine clinical use of HES-containing medicinal products of Fresenius Kabi will be documented by retrospective data collection from patient charts within a predefined timeframe. Retrospective data collection best reflects actual patterns of use and allows reducing bias as described in Section 9.9 to a minimum. To ensure that there is a very high coverage of patients administered HES containing products, site selection will focus on sites using electronic PDMS. Patient charts will be thoroughly searched via free text, ICD-10 code (diagnosis), and ATC code (medication) to ensure identification of eligible patients as complete as possible.

Following the final approval of the submitted protocol by the PRAC, notification to NCAs and positive IEC opinion as required by national and local regulations and requirements, as well as the administrative processes such as site selection and contracting of sites will be initiated.

The retrospective data collection will comprise patient chart data of patients who have been treated between January 1st, 2015 and May 1st, 2015. Patient chart data will be collected going backwards in a predefined timeframe, e.g. of one week (depending on the results of the site feasibility), starting May 1st, 2015 (calendar week 18). All patients treated with HES-containing products of Fresenius Kabi during this week should be documented. In the event that the predefined number of patients per site is not achieved within e.g. this week, data collection can be extended e.g. week by week (again going backwards) until the number of predefined patients has been reached, but not beyond January 1st, 2015. All patients treated with HES-containing products of Fresenius Kabi within the predefined timeframe are documented in the DUS and followed-up until the start and end of HES therapy, even if the start or end of HES therapy are outside the predefined timeframe.

Data collection will include relevant demographic data, main diagnosis at hospital admission, indication for HES use, posology (dosage), and co-morbidities.

The parameters as listed in Section 9.3 will be documented.

9.2 Setting

The setting is any hospital in the countries specified in Section 9.2.1 using any HES product of Fresenius Kabi and willing to document all HES treated patients within the predefined timeframe.

9.2.1 Countries, Feasibility and Site Selection

The DUS is intended to be conducted in the following European Member States: Belgium, Czech Republic, France, Germany, Netherlands, Poland, Spain, Sweden, United Kingdom. In order to reduce potential bias from site specific clinical practice it is aimed that per country, at least 5 sites will be included expecting a minimum of about 67 eligible patients per site (depending on the outcome of the feasibility). The sites can only participate upon agreeing to the requested procedures in the participating sites as specified in Section 9.8.1.

Prior to the start of the DUS, a feasibility check/survey will be performed by the CRO to evaluate e.g.

- whether the sites use HES-containing medicinal products from Fresenius Kabi,
- how frequently HES-containing medicinal products from Fresenius Kabi have been used,
- whether the sites use electronic PDMS,
- whether all wards or, if this is not the case, which wards in the hospitals use electronic PDMS,
- which wards have been supplied with HES from Fresenius Kabi within the sites,
- whether the sites collect general consent for using patients' data for research projects,
- whether the sites are willing to participate.

For the retrospective data collection in this DUS, sites using electronic PDMS will be preferred since PDMS allow the comprehensive review of all patient charts at the site regarding administration of HES products in the given retrospective data collection period. Thus, the selection process for sites using HES-containing medicinal products from Fresenius Kabi will be performed following a hierarchic stepwise process as described below:

(1) HES use and full PDMS coverage within data collection period
(2) HES use and PDMS use in all wards which have been identified in the survey to be supplied with HES within data collection period
(3) HES use and PDMS use or paper documentation in all wards which have been identified in the survey to be supplied with HES within data collection period (applies to sites with partial PDMS coverage in HES using wards)
(4) Sites or wards with HES use within data collection period but paper documentation only

For sites not (completely) using PDMS, the sites' pharmacies will be contacted by the CRO, as part of the feasibility check/survey, to identify the wards which had been supplied with HES from Fresenius Kabi to ensure a high coverage of patients that had received HES. This procedure and the results will be thoroughly documented by the CRO.

After each selection step as described above, identified study sites will be randomly selected per country in case the selection process reveals more than the intended total number of sites.

If despite all above mentioned selection strategies the required number of about 334 patients per country cannot be documented within the predefined timeframe, the following measures will be taken in a further hierarchic stepwise manner:

(A) Extension of timeframe for data collection until November 1st, 2015 (if retrospective nature of the DUS is still ascertained)
(B) Initiation of new sites in the respective country where 334 patients have not been documented
(C) Inclusion of additional European countries that have not yet participated and fulfilling the selection criteria (e.g. minimum of 5 centres and sufficient patients)

All new countries and all new sites will be selected according to the feasibility criteria as described above.

All available data, including those from an initially included country where the required patient and/or site number could not be finally achieved, will be analysed in a descriptive manner.

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 in clinical practice.

The retrospective review of patient data in the identified sites will start about 3 to 4 months after protocol approval by the PRAC, final site selection and notification to NCAs and positive IEC opinion as required by national and local regulations and requirements.

9.2.3 Inclusion Criteria

- Patients who were receiving any of the HES-containing medicinal products listed in Annex 1a within the predefined timeframe will be documented in the DUS.

9.2.4 Exclusion Criteria

- Patients who were included in interventional clinical trials treating patients with HES-containing products within the predefined timeframe.

  Patients who were treated with HES within an interventional clinical trial are excluded since a clinical trial protocol may require study specific use outside clinical routine practice.

9.3 Variables

9.3.1 HES Usage in the Hospital

Data on the "HES usage in the hospital" are documented in an eCRF and will be used for assessing the coverage of patients that had received HES products of Fresenius Kabi (see Section 9.2.1).

The parameters regarding the HES usage of Fresenius Kabi will be assessed as follows:

- Hospital
  - Name
  - Address

- Estimated average HES amount used per week in:
  - Hospital (total amount in study site)
  - Intensive Care Unit (ICU) (if various, specify)
  - Paediatric Intensive Care Unit (PICU)
  - Operating room
  - Surgical ward
  - Intermediate care
  - Emergency unit
  - Burns unit
  - Other (please specify)

Data on the estimated use of HES products of Fresenius Kabi will be based on the supplied amount of HES as reported by the hospital pharmacy or hospital´s HES supplier.

9.3.2 Anonymised Patient Specific Variables

Below listed parameters are documented in the eCRF. A high validity and accurateness of these parameters is expected as their documentation is part of clinical routine and they are essential for therapeutic decisions and reimbursement.

To evaluate the effectiveness of risk minimisation measures via assessing the adherence of hospital physicians to the revised European PI of HES-containing medicinal products concerning indication, posology (dosage) and contraindications, various parameters will be assessed. These are as follows:

Basic Assessment

- Hospital (name, address)
- Patient admission date (calendar week, year)

- Ward(s) where HES of Fresenius Kabi was administered
  - ICU (if various, specify)/PICU/Operating room/Surgical ward/Intermediate care/Emergency unit/Burns unit/Other

- Demographic data
  - Age (< 18 years or ≥ 18 years)
  - Weight

- Main diagnosis at hospital admission (ICD-10 code plus corresponding plain diagnosis text)

- Indication for HES use
  - Treatment of Hypovolaemia due to acute blood loss (yes/no)
  - Treatment of Hypovolaemia without acute blood loss (yes/no)
  - HES used exclusively for "Prophylaxis of Hypovolaemia" and not for "Treatment of Hypovolaemia" (yes/no)
  - Other (yes/no; if yes ICD-10 code)

Relevant Co-Morbidities Before HES Administration

Operational definitions for the below listed variables (co-morbidities) are given in Annex 5, apply for this DUS only and must be considered when the information for the respective variable is to be entered in the eCRF from patient charts.

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

- Burns (yes/no)

- Disturbed fluid status (yes/no)
  - Dehydration (yes/no)
  - Hyperhydration (yes/no)

- Severe hyperkalaemia (yes/no)

- Severe hypernatraemia (yes/no)

- Severe hyperchloraemia (yes/no)

- Congestive heart failure (yes/no; if yes: NYHA stage)[4]

- Pulmonary oedema (yes/no)

- Severely impaired hepatic function (yes/no)

- Renal failure
  - Renal impairment (yes/no)
  - Renal replacement therapy (yes/no)

- Severe coagulopathy (yes/no)
- Systemic inflammation
  - Sepsis (yes/no)
  - Severe sepsis (yes/no)
  - Septic shock (yes/no)
- Clinically relevant intracranial/cerebral bleeding (yes/no)
- Organ transplant patient (yes/no)
  - Acute organ transplant patient (yes/no)
  - Date of transplantation, if available (calendar week, year)

HES Administration Prior to Admission to the Hospital (DUS Study Site)

- HES administration at day of admission or preceding day before admission to the hospital (yes/no/no information available);
  if yes:
  - Place/institution [hospital, ambulance, other],
  - Trade name of any prescribed HES product
  - Posology (Dosage)
    - HES infusion (first to last bag/bottle)
      - Start of infusion (Day 1/Time hh:mm)
      - Total amount infused (ml)
      - End of infusion (Day X/Time hh:mm)

HES Administration in the Hospital (DUS Study Site)

- Trade name of prescribed HES product
- Posology (Dosage)
  - HES infusion (first to last bag/bottle)
    - Start of infusion (Day Y/Time hh:mm) of each bag/bottle
    - Amount infused (ml) of each bag/bottle
    - End of infusion (Day Z/Time hh:mm) of each bag/bottle

At Completion of HES Administration

- Date of discharge from treating ward (calendar week, year)

9.4 Data Sources

Data entry based on patient charts, preferably from electronic PDMS, will be performed by the investigators or delegated responsible persons at the participating site using the online eCRFs.

The eCRFs will be structured according to the parameters described in Section 9.3.

9.5 Study Size

For determining the number of patients that should be documented in this DUS it is aimed to achieve sufficient precision of estimates for the percentage of non-compliance to the PI. It is intended that all analyses will be performed for the overall population as well as for each country separately. Therefore, the chosen sample size needs to have sufficient precision also for the country-specific estimates.
For potential non-compliance rates in the interval of 1 % to 4 % the expected precision (95 % confidence intervals) for various sample sizes ranging from 100 to 3000 patients were calculated. The results are shown in Table 1.

Table 1: Expected 95 % confidence intervals for potential non-compliance rates in the intervals of 1 % to 4 % estimated in sample sizes of 100 to 3000 patients. Exact method (R function binom.test{stats}) used.

	Estimated rate 1 %	Estimated rate 2 %	Estimated rate 3 %	Estimated rate 4 %
N = 100	0.0 - 5.4 %	0.2 - 7.0 %	0.6 - 8.5 %	1.1 - 9.9 %
N = 334	0.2 - 2.6 %	0.8 - 4.3 %	1.4 - 5.4 %	2.1 - 6.6 %
N = 500	0.3 - 2.3 %	1.0 - 3.6 %	1.7 - 4.9 %	2.5 - 6.1 %
N = 1000	0.5 - 1.8 %	1.2 - 3.1 %	2.0 - 4.3 %	2.9 - 5.4 %
N = 1500	0.6 - 1.6 %	1.4 - 2.8 %	2.2 - 4.0 %	3.1 - 5.1 %
N = 2000	0.6 - 1.5 %	1.4 - 2.7 %	2.3 - 3.8 %	3.2 - 5.0 %
N = 2500	0.6 - 1.5 %	1.5 - 2.6 %	2.4 - 3.7 %	3.3 - 4.8 %
N = 3000	0.7 - 1.4 %	1.5 - 2.6 %	2.4 - 3.7 %	3.3 - 4.8 %

Considering the number of patients that is expected per country, it is intended to include at least 3000 patients in total (meaning 334 patients per country) in order to achieve sufficient precision of also country-specific estimates.
As an example, for an assumed non-compliance rate of 3 % and a sample size of 334 patients the expected 95 % confidence interval is 1.4 % to 5.4 %. For the intended sample size of overall 3000 patients the expected 95 % confidence interval is 2.4 % to 3.7 %.

9.6 Data Management

9.6.1 Database

Data entered on the eCRF will be stored centrally into a database, which is maintained according to current standards for hard- and software security, including daily backups and access to the data files only for qualified staff involved in the DUS. For the DUS study sites,

the CRO will assign a secure login for each member of staff in the site who has responsibility for data collection (e.g. physician or delegated responsible person) after request from the principal investigator who is responsible for the study.

9.6.2 Patient Data Anonymisation

Patient data investigated will be de-identified in an unlinked manner to personal identifier. The documented data are restricted to personal identifier, patient age range (< 18 years or ≥ 18 years), medical procedures, diagnostic codes according to ICD-10, and name, dose, and duration of supply of prescribed HES product (and other drugs, if applicable). The full list of anonymised patient specific variables is specified in Section 9.3.2.

Fresenius Kabi will in no way be able to backtrace the identification of any study subject.

9.7 Data Analysis

9.7.1 Descriptive Data

Because of the exploratory character of this study only descriptive statistics will be performed. All parameters (see Section 9.3) will be presented as mean ± standard deviation for continuous normally distributed variables and median (25^{th}; 75^{th} percentile) for ordinal and continuous non-normal (skewed) variables. Categorical variables will be presented as percentage (and 95 % confidence interval). All analyses will be performed for the overall population as well as for each country separately. All data will be examined for the overall population and subgroups (each site/country separately) specified by indication and contraindications according to the revised PI (as listed in Annex III of the EC decision).

The number of patients (including percentage, 95 % confidence intervals) receiving HES-containing medicinal products that do not adhere to the specifications made in the revised PI will be examined.

Cumulative and maximum daily dose will be calculated for analysis of exposure to HES products.

Coverage of HES treated patients (i.e. the estimated proportion of all HES administrations that are included in the DUS population in each site) will be estimated for each site. The variable 'average HES amount used per week' will be used to estimate the total HES population treated with products of Fresenius Kabi of each site, which is the denominator of the coverage rate.

Missing data in the eCRF will be detected via automatic edit checks by the electronic data capture system, during data entry, to assess whether the information is available in the PDMS or patient chart. Data that remain missing will not be imputed in the statistical analyses.

Prior to database closure a detailed statistical analysis plan (SAP) will be written to describe how the data will finally be analysed.

9.7.2 Validity of Outcome Measures

Assessing adherence to the PI specifications in a non-interventional and retrospective DUS will reduce bias to a minimum. In contrast to a prospective setting, the retrospective design of the DUS will not influence the clinical practice but will discover any in-label as well as off-label use.

The inclusion of several countries, study sites and the requirement of inclusion of all identified, HES-treated patients with products of Fresenius Kabi within a predefined timeframe, as well as the dedicated data acquisition in this DUS preferably by electronic PDMS, should provide a comprehensive record of HES-containing medicinal products used in routine clinical practice over all involved investigational sites.

9.8 Quality Control

To ensure reliable data quality, procedures will follow the recommendation by the Agency for Healthcare Research and Quality (AHRQ)[5] in 2010 as specified below.

9.8.1 Procedures in the Participating Sites

Each site designates one principal investigator for this DUS. He/she will be supported by the appointed CRO and will be responsible for:

- Obtaining local Ethics Committee approval (if required by local requirements) for the conduction of the DUS in his/her site.
- Obtaining a waiver for signed written patient data protection consent if required according to site/national policy.
- Distributing login of the (online) eCRFs together with corresponding training of all site staff involved in the data acquisition.
- Ascertainment of data accuracy, i.e. he/she is responsible for a complete recording of data in the (online) eCRFs in the respective site.
- Notification to the CRO, in advance of data collection and at any time after start of data collection, if the retrospective recording is not or no longer possible or feasible (e.g. due to changes in the resource situation in the participating site).

Depending on national and local requirements, the CRO will facilitate tasks for the principal investigator, e.g. by compiling documents for IEC approval, providing training material and detailed lists of missing or inconclusive data recorded in the eCRF.

Based on local requirements specific training for each site will be provided.

Each participating site will receive an Investigator Site File from the CRO prior to the start of the DUS, containing the following documents:

- DUS protocol
- Short overview of the DUS
- Manual for (online) eCRFs
- Documents for Ethics Committee opinion
- Training slides for investigators and delegated responsible persons
- Login to the eCRFs and an electronic version of all files from the CRO.

To limit bias with regard to possible changes in treatment behaviour concerning the actual use of HES-containing medicinal products, the full set of study documents/information (e.g. all Site Initiation related documents, Trainings, Investigator Site Files) will not be provided to the sites before May 1st, 2015.

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

As far as possible, data will be checked automatically for completeness and accuracy on entry into the eCRFs (plausibility check by means of automatic queries). Missing or implausible values are highlighted and the staff member(s) in the participating sites will be prompted to confirm the correctness and completeness of the entered data.

All requests to complete missing data fields in the eCRF will be shown during data entry to the sites by the electronic data capture system, so that sites can readily access individual patient data to complete data if necessary.

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

All data will be prepared, anonymised 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 performing eCRF training and providing all relevant documentation to the investigator and delegated responsible persons at each site as specified in Section 9.8.1.

9.9 Limitations of the Research Methods

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

- The retrospective design may lead to an underestimation of amounts of HES products of Fresenius Kabi given due to incomplete data documentation.
- Source data verification of the data by the CRO by reviewing the individual patients' original medical records will not be possible.
- There is a certain unavoidable bias possible due to the hospital selection strategy.

- The total amount of sites having electronic PDMS implemented or having PDMS only partially implemented may affect the study timelines. In particular low PDMS coverage in sites might negatively impact the study timelines.

9.10 Other Aspects

The development of the DUS protocol is based on the following guideline:
"Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies" 26 September 2012; EMA/623947/2012; Patient Health Protection[6]

10. Protection of Human Subjects

This DUS is a retrospective, non-interventional study documenting 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 anonymisation measures to ensure confidentiality.

The DUS will be conducted in accordance with the protocol, the Declaration of Helsinki[7], Good Pharmacovigilance Practice (GVP)[8], Good Pharmacoepidemiology Practices (GPP)[9] and any applicable local regulations. Special attention will be paid to data protection laws, adhering to EU directive on data protection[10].

To safeguard confidentiality of direct patient related data, no personal identifiers will leave the study sites. The responsible Ethics Committees will be fully informed about the intended retrospective data collection in the course of this DUS. Depending on national law and local regulations review and opinion of the DUS will be obtained from the responsible Ethics Committees. This protocol will be submitted to Ethic Committees with a request to waive informed consent according to the International Society for Pharmaceutical Engineering (ISPE) guideline on data privacy standard, Section IV[11].

Obtaining retrospectively informed consent to use data from charts review for research purposes is considered impracticable. If waiving informed consent is not possible, which is considered to be unlikely, the respective site for which waiving is not possible will therefore not be selected, as otherwise patient inclusion may be hindered substantially and the risk of patient selection bias based on the potentially limited receipt of informed consents may increase.

10.1 Independent Ethics Committees (IECs)

According to applicable regulations, Fresenius Kabi, the appointed CRO, or the responsible site will:

- notify or obtain opinion from the relevant IEC of the protocol, and any amendments,
- request to waive informed consent according to the ISPE guideline on data privacy standard, Section IV (see Section 10 of the DUS protocol).

Fresenius Kabi, the appointed CRO, or the principle investigator will submit required documents to the IEC, such as (only if applicable):

- periodic updates on the progress of the study,
- notification of the end-of-study,
- a summary of the study results, 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 IEC and will provide the study site with a copy of this list.

10.2 National Competent Authorities (NCA)

If required according to local regulations, the NCA and/or other national or regional authorities will be notified about the DUS and provided with the required documents for approval, if needed. An updated list of submission and approval dates and a copy of all documents submitted will be kept.

11. Management and Reporting of Adverse Events/Adverse Reactions

In line with the implementing Regulation 520/2012, a Drug Utilisation Study (DUS) is considered a post-authorisation safety study (PASS).
This DUS is designed to describe pattern-of-use for HES-containing products. In line with GVP Module VI[12], non-interventional post-authorisation studies based on secondary use of data, as in this DUS with HES-containing medicinal products, using retrospective data collection, do not require the reporting of suspected adverse reactions in the form of Individual Case Safety Reports to national authorities.
In line with the target of this DUS, overdose, abuse, off-label use, misuse, and medication error will be documented in the eCRF, coded according to MedDRA and reported in the final study report. In addition, these findings will be considered in Periodic Safety Update Reports as applicable (see GVP Module VI[12]).

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.6.3.2[8] as well as the *"Guidance for the format and content of the final study report of non-interventional post-authorisation safety studies, 30 July 2013"*[13]. The Final Study Report should be available and submitted within 24 months after approval of the final protocol by the PRAC. The participating sites will be informed about the results when the report is finalised. According to the pharmacovigilance legislation, which came into effect in 2010, an abstract of the study results is intended to be published in a publicly available EU PAS register.[14]

13. References

1 Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl Starch 130/0.42 versus Ringer's Acetate in Severe Sepsis. N Eng 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 Classes of Heart Failure as referenced under the given weblink: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp (accessed Dec 01, 2014)

5 Gliklich RE, Dreyer NA, eds. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September 2010.
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at:
http://www.ncbi.nlm.nih.gov/books/NBK49444/pdf/TOC.pdf (accessed May 14, 2014)

6 Guidance for the format and content of the protocol of non-interventional post-authorisation safety studies, 26 September 2012, EMA/623947/2012, Patient Health Protection
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at the given weblink (accessed May 14, 2014):
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/10/WC500133174.pdf

7 World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191-4. DOI: 10.1001/jama.2013.281053

8 Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 1) - EMA/813938/2011 Rev 1
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at the given weblink (accessed May 14, 2014):

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf

9 ISPE. Guidelines for Good Pharmacoepidemiology Practices (GPP) Pharmacoepidemiol Drug Saf. 2008 Feb;17(2):200-8.
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at the given weblink (accessed Oct 30, 2014):
http://www.pharmacoepi.org/pub/1c2a23af-2354-d714-516a-7175549e3a88

10 Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data. Official Journal of the European Communities L281/31 23.11.1995
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31995L0046&from=EN (accessed May 14, 2014)

11 ISPE Guideline "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 Nov 4, 2014):
https://www.pharmacoepi.org/resources/privacy.cfm#_Toc430151877

12 Guideline on Good Pharmacovigilance Practices (GVP) – Module VI (Rev 1) - EMA/873138/2011 Rev 1
Due to copyright legislation a copy of this reference cannot be provided. However, it is freely available at the given weblink (accessed Oct 30, 2014):
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14 Temporary EU PAS Register (E-Register), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP), as accessible at the given weblink (accessed Dec 01, 2014):
http://www.encepp.eu/encepp/studiesDatabase.jsp

Annex 1 List of Stand-Alone Documents

Number	Document reference number	Date	Title
Annex 1a	Annex 1a, Version 1.1	17 Apr 2015	List of HES-containing medicinal products registered in those countries in which DUS is performed (Fresenius Kabi Deutschland GmbH)
Annex 1b	Annex 1b, Version 1.2	04 May 2015	HES DUS participating site and investigator list

Annex 2 ENCePP Checklist for Study Protocols

Annex 3 Additional Information

- Annex III of the final implementing decision, issued by the European Commission (EC) on December 19, 2013

Annex 4 Signature Pages

Annex 5 Operational Definitions for "Relevant Co-Morbidities Before HES Administration"