Challenges in Conducting a Multinational European Study of Severe Hypersensitivity Reactions Among Recipients of Intravenous Iron

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CONFLICTS OF INTEREST

- This study is funded by a consortium of IV iron manufacturing companies through a contract with RTI Health Solutions (RTI-HS) that funds all other participating research centers. The contract provides the research team independent publication rights.
- RTI-HS is an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.
- The PHARMO Institute of Drug Outcomes Research is an independent research institute that performs financially supported studies for government and related health care authorities and pharmaceutical companies.
- The Bordeaux PharmacoEpi platform, INSERM CIC1401 of Bordeaux University, is an independent nonprofit research organization that does work for government agencies and pharmaceutical companies.
- The Centre for Pharmacoepidemiology, Karolinska Institutet receives grants from pharmaceutical companies, regulatory authorities, and contract research organizations for performance of drug safety and drug utilization studies.
- AT is a staff member of Carl von Ossietzky University of Oldenburg. She has conducted research funded by pharmaceutical companies.
- Aarhus University receives institutional funding for research projects from several public and private entities.
- GvG, MS, and KR are employees at the Department of Internal Medicine–QiN-group, University of Cologne, Faculty of Medicine and University Hospital Cologne, Germany.
- The Leibniz Institute for Prevention Research and Epidemiology–BIPS occasionally conducts studies financed by the pharmaceutical industry, mostly PASS requested by health authorities.
- JD is an employee of the Information System for Health Care Data (Data Transparency), which processes applications from RTI-HS and charges user fees.
- MF is an employee of PrimeVigilance, a service provider specializing in pharmacovigilance services and consulting. PrimeVigilance received a honorarium from a consortium of manufacturers of intravenous iron compounds for the coordination of the scientific committee.

BACKGROUND

- Severe hypersensitivity reactions (SHRs) in intravenous (IV) iron treatment are rare and a poorly characterized safety concern in Europe. A multidatabase study approach is required to evaluate this rare outcome. A regulatory-mandated postauthorization safety study (PASS) with multiple sponsors will assess the risk of SHRs in IV iron users in Europe (EUPAS 20720). Results will be available in 2020.

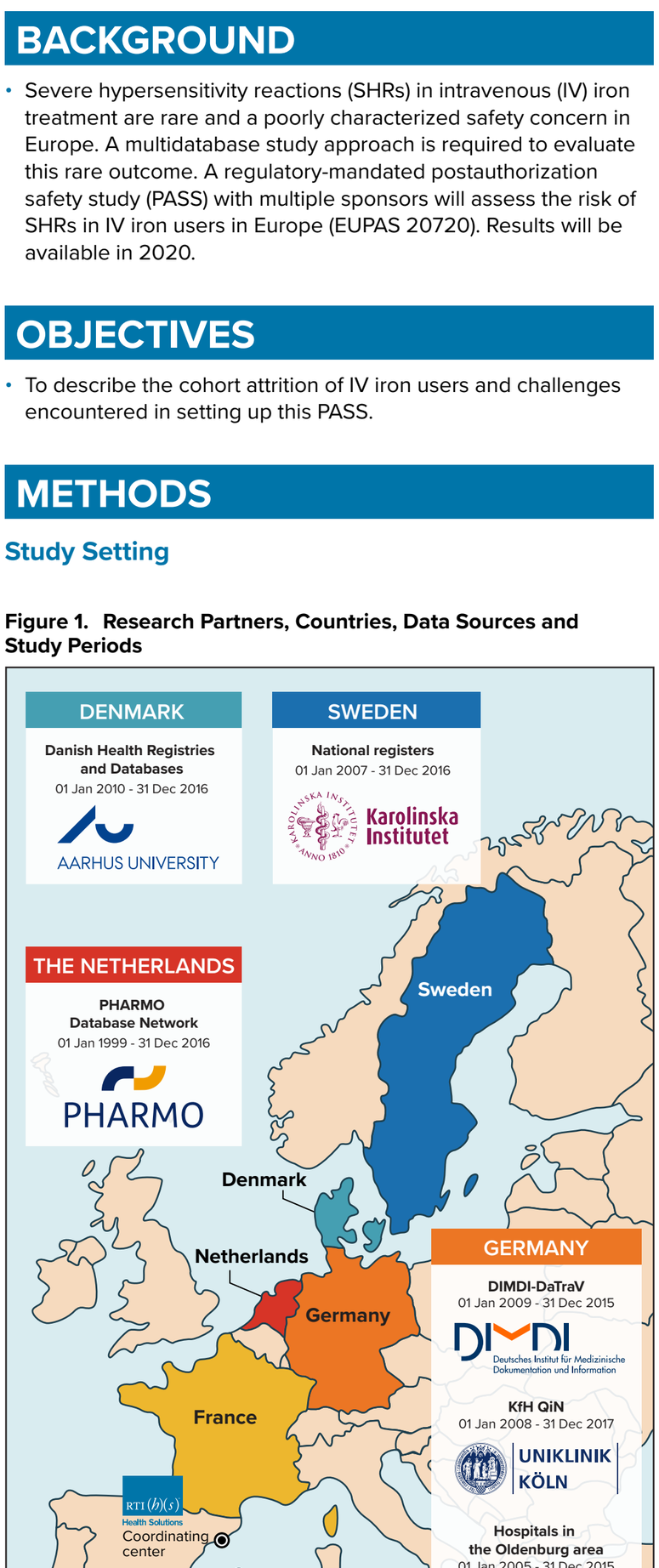
OBJECTIVES

- To describe the cohort attrition of IV iron users and challenges encountered in setting up this PASS.

METHODS

Study Setting

Figure 1. Research Partners, Countries, Data Sources and Study Periods



DIMDI-DaTraV = Information system for health care data (data transparency) of the German Institute of Medical Documentation and Information; GePaRD = German Pharmacoepidemiological Research Database; SNDS = National Health Care Insurance System Database; KfH QiN = registry of the KfH – Board of Trustees for Dialysis and Kidney Transplantation Quality in Nephrology programme.

Study Design

- Cohort study of users of IV iron and IV penicillins
- Study population: eligible patients with a record of IV iron treatment during the study period (iterative).
  - Inclusion criteria:
    - Aged 18 years or older at cohort entry date
    - Continuous enrollment for at least 12 months before the cohort entry date
  - Exclusion criteria: Concurrent administration within the risk window of:
    - > 1 type of IV iron and/or
    - an IV iron compound and an IV penicillin
- The risk of SHRs due to penicillin administration has been described in the literature. A cohort of IV penicillin users was used, where feasible, to assess the performance of the SHR identification algorithm.
- The algorithms used to identify SHRs rely on both diagnostic codes and SHR markers (e.g., symptoms, signs, and treatments)
- Harmonization and local adaptation of outcomes and variable definitions across all research centers was performed.
- Distributed analyses were conducted in each database using a common protocol and analysis plan with local adaptations.

Figure 2. Study Design

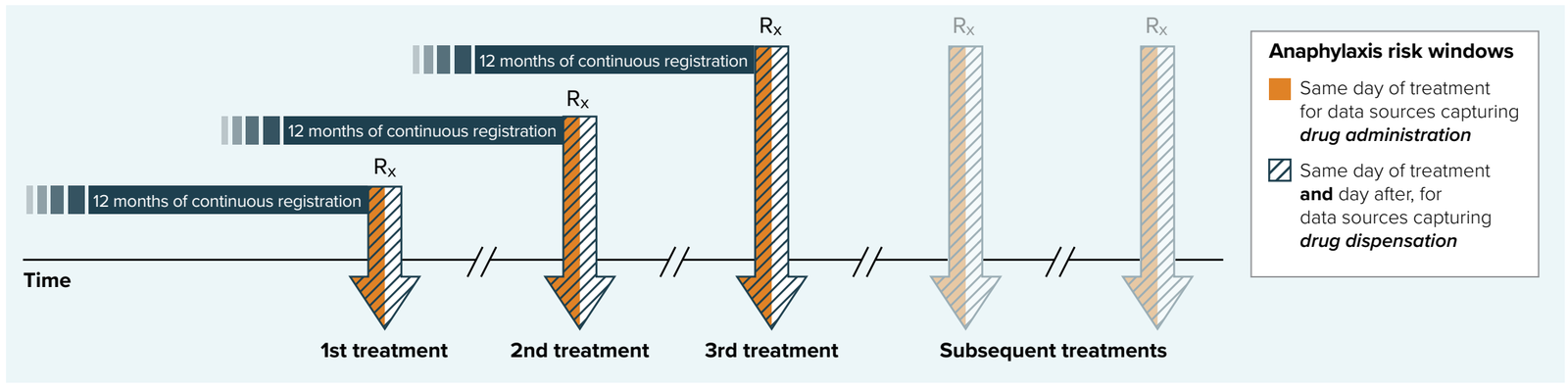


Figure 3. Event-Finding Algorithm

A — CRITERION A

INPATIENT SETTING

Specific anaphylaxis codes

T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered)

OR

T80.5 (anaphylactic shock due to serum)

OR

T78.2 (anaphylactic shock, unspecified) (i.e., the reason for admission, if this information is available)

OR

B — CRITERION B

OUTPATIENT SETTING

Specific anaphylaxis codes

T88.6 (anaphylactic shock due to adverse effect of correct drug or medicament properly administered)

OR

T80.5 (anaphylactic shock due to serum) **OR T78.2** (anaphylactic shock, unspecified)

AND

A code for one or more of the following symptoms, procedures, or treatments:

- Bronchospasm (J98.01, acute bronchospasm)
- Stridor (R06.1)
- Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)
- Angioedema (T78.3 angioneurotic oedema)
- Admission/transfer to intensive care unit (health encounter codes as available in each data source)
- Epinephrine/adrenaline (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)
- Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs); injection of corticosteroids (Y42.0, glucocorticoids and synthetic analogues)
- Oxygen (T41.5 therapeutic gases or other data source–specific procedural codes for oxygen administration, as appropriate)
- Cardiac arrest with successful resuscitation (I46.0); cardiac arrest, unspecified (I46.9)

OR

C — CRITERION C

INPATIENT SETTING

Unspecific hypersensitivity codes

T88.7 (unspecified adverse effect of drug or medicament)

OR

T78.4 (allergy unspecified)

OR

Y44.0 (adverse effects in therapeutic use: iron preparations and other antihypochromic-anaemia preparations) (i.e., the reason for admission, if this information is available)

AND

A code for one of the following symptoms, procedures, or treatments:

- Bronchospasm (J98.01, acute bronchospasm)
- Stridor (R06.1)
- Angioedema (T78.3 angioneurotic edema)
- Injection of diphenhydramine (Y43.0, antiallergic and antiemetic drugs); injection of corticosteroids (Y42.0, glucocorticoids and synthetic analogues)
- Oxygen (T41.5 therapeutic gases or appropriate procedural codes for oxygen administration)

AND ALSO

A code for one of the following symptoms, procedures, or treatments:

- Hypotension (I95.0, idiopathic hypotension; I95.2, hypotension due to drugs; I95.81, other hypotension, postprocedural; I95.89, other hypotension; I95.9, hypotension unspecified)
- Epinephrine/adrenaline (Y51.4, predominantly alpha adrenoreceptor agonists; Y51.5, predominantly beta-adrenoreceptor agonists, not elsewhere classified; or Y51.9, other and unspecified drugs primarily affecting the autonomic nervous system)
- Admission/transfer to intensive care unit (health encounter codes as avaiable in each data source)
- Cardiac arrest with successful resuscitation (I46.0); cardiac arrest, unspecified (I46.9)

RESULTS

Table 1. IV Iron Treatment and Severe Hypersensitivity Reactions (Preliminary)

IV Iron Treatment[a] and SHR Events (n)	Central Denmark Region Database	SNDS Database, France	PHARMO, Netherlands	Swedish National Registers	GePaRD, Germany	KfH QiN, Germany	DIMDI-DaTraV Database, Germany	Overall
First IV iron treatment								
Patients	5,860[b]	75,512	5,875	42,468	140,916	33,619	Pending	304,250
Events (preliminary)[c]	< 5	0	0	< 5	9	0	Pending	min 13, max 16
Second IV iron treatment								
Patients	2,150[b]	22,626	1,855	20,822	67,895	32,756	Pending	148,104
Events (preliminary)[c]	0	0	0	< 5	< 5	0	Pending	3
Third or subsequent IV iron treatment								
Patients (IV iron treatments)	1,420 (34,760)[b]	11,597 (58,298)	913 (3,217)	11,771 (37,471)	47,789 (348,945)	32,144 (2,620,795)	Pending	10,634 (3,103,486)
Events (preliminary)[c]	0	0	0	0	10	0	Pending	10

[a] Treatment ascertained through either administration, prescription, or dispensing records.
[b] Numbers were rounded up to the nearest 10 due to data protection rules.
[c] Severe hypersensitivity reaction events were identified as potential study cases through the main case-identification algorithm and recorded "within the predefined time risk window."
Note: Data counts between 1-4 are not reported to comply with data protection rules in some data sources.

Table 2. IV Penicillin Treatment and Severe Hypersensitivity Reactions (Preliminary)

IV Penicillin Treatment[a] and SHR Events (n)	Danish Central Region EMR Database	SNDS Database, France	PHARMO, Netherlands	Swedish National Registers	GePaRD, Germany	KfH QiN, Germany	DIMDI-DaTraV Database, Germany	Overall
First IV penicillin treatment								
Patients, first treatment	116,980[b]	57,200	39,002	NA	18,112	NA	Pending	231,294
Events[c] (preliminary)	17	< 5	< 5	NA	6	NA	Pending	27
Any IV penicillin treatment								
Patient treatments, any	736,070[b]	78,292	114,639	NA	54,999	NA	Pending	984,000
Events[c] (preliminary)	29	< 5	< 5	NA	8	NA	Pending	43

NA = not applicable.
[a] Treatment ascertained through either administration, prescription, or dispensing records.
[b] Numbers were rounded up to the nearest 10 due to data protection rules.
[c] Severe hypersensitivity reaction events were identified as potential study cases through the main case-identification algorithm and recorded "within the predefined time risk window."
Note: Data counts between 1-4 are not reported to comply with data protection rules in some data sources.

CONCLUSIONS

- Sizeable numbers of IV iron users have been identified.
- Drug exposure is captured through prescription, dispensing, or administration records from hospital or outpatient settings, but complete exposure capture was not possible in any country.
- The numbers of SHRs identified among IV iron users are lower than reported in recent studies from the United States.[1,2]
- Understanding the commonalities and differences of the data available in the collaborating centers and aligning variable definitions are critical to conducting a multidatabase study.

REFERENCES

1. Walsh K, Andrade S, Cocoros N, Forrow S, Kane R, Lehman-White N, et al. Sentinel assessment report: parenteral iron and anaphylactoid reactions. US Food and Drug Administration; 22 July 2016. Available at: https://www.sentinelinitiative.org/sites/default/files/surveillance-tools/routine-querying/Sentinel_Parenteral-Iron-and-Anaphylactoid-Reactions_Report.pdf Accessed May 20, 2019.
2. Wang C, Graham DJ, Kane RC, Xie D, Wernecke M, Levenson M, et al. Comparative risk of anaphylactic reactions associated with intravenous iron products. JAMA. 2015 Nov 17;314(19):2062-8.

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The power of **knowledge**.
The value of **understanding**.

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