Post Authorization Safety Study (PASS) Information

Acronym/Title	Safety profile of Ultravist in children and elderly (UV Age)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	PASS / Phase IV
EU PAS register number	Study not yet registered
Active substance	Radiological / Low Osmolar non-ionic Contrast Medium (LOCM), (V08AB05) iopromide
Medicinal product	Ultravist
Product reference	Not applicable
Procedure number	Not applicable
Study Initiator and Funder	Bayer AG
Research question and objectives	To describe the risk of hypersensitivity reactions to Ultravist specifically in children (≤19 years of age) and elderly patients (≥60 years), compared to those in the middle age group (20-59 years).
Country(-ies) of study	37 countries including Europe (mostly Germany and Spain), Asia (mostly China and South Korea) and USA.
Author	PPD

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD

The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
CI	Confidence Interval
CRF	case report form
DMR	Data Management Report
HEOR	Health Economics and Outcomes Research
i.a.	intra-arterial
i.v.	intra-venous
IRB	Institutional Review Board
LOCM	low osmolar non-ionic contrast medium
MedDRA	Medical Dictionary for Regulatory Activities
N/A	Not Applicable
OS	Observational Study
PASS	Post-Authorization Safety Study
PT	Preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System organ class
QPPV	Qualified Person Responsible For Pharmacovigilance

3. Responsible parties

3.1 Study initiator and funder

Role:	OS Conduct Responsible
Name:	PPD
Role:	Qualified Person responsible for Pharmacovigilance (QPPV)
Name:	PPD
Role:	OS Medical Expert
Name:	PPD
Role:	OS Statistician
Name:	PPD
Role:	OS Epidemiologist
Name:	PPD
Role:	OS Safety Lead
Name:	PPD
Role:	MAH contact person (Regulatory Affairs)
Name:	PPD
Contributing Medical Experts	PPD

Contact details of the responsible parties at Bayer AG are available upon request.

3.2 Collaborator(s)/External partner(s)/Committee(s)

n.a.

4. Abstract

Acronym/Title	Safety profile of Ultravist in children and elderly (UV Age)
Study type / Study phase	PASS / Phase IV
Authors	PPD
Rationale and background	Ultravist is on the market for >35 years and has been administered >276 million times. While the general safety profile, including risk of hypersensitivity reactions has been widely investigated, data is limited for the age groups of children (≤19 years of age) and elderly (≥60 years).
Research question and objectives	To describe the risk of hypersensitivity reactions to Ultravist specifically in children (≤19 years of age) and elderly patients (≥60 years), compared to those in the middle age group (20-59 years).
Study design	Nested Case-Control analysis in a pooled cohort of 4 non-interventional studies with Ultravist
Population	Patients undergoing contrast enhanced CT scan or angiographic procedures for various indications who received Ultravist.
Variables	Hypersensitivity reactions, demographic variables, comorbidities, indication, mode of CM administration, dose, iopromide concentration, pre-medication, geographic region
Data sources	Four company sponsored non-interventional studies with iopromide
Study size	152,233 records of patients
Data analysis	Cases of hypersensitivity reactions will be identified following a preset case definition. Controls are patients without any adverse event (AE) after the contrast administration. Logistic regression will be used to analyse the data with adjustment for potential confounders: sex, history of adverse reactions, mode of administration etc. The entire planned analysis will be described in a statistical analysis plan, which will be finalized before the analysis starts.

5. Amendments

None

6. Milestones

Table 1: Milestones

Milestone	Planned date
Start of analysis	QIV 2020
End of data collection	n.a.
Registration in the EU PAS register	QIII 2020
Final report of study results	QII 2021

7. Rationale and background

Ultravist (iopromide) is a low osmolar non-ionic contrast medium (LOCM) with the active ingredient iodine (1, 2). Ultravist has been on the market for >35 years (first marketed on February 28, 1985). As of June 30, 2019, about 276 Mio administrations have been applied. It is currently used in more than 108 countries and is administered to >15 million patients per year.

The overall safety, including rare hypersensitivity reactions, has been shown in numerous studies (3-6). Kopp et al. reported 11 serious adverse drug reactions (ADR) considered as hypersensitivity reactions to Ultravist in a post-marketing surveillance study in 74,717 patients (3).

Mortele et al. prospectively recorded all adverse events (AEs) in a cohort of 29,508 consecutive patients in a hospital setting over 2 years (4). The overall incidence of AEs was 0.7%, with 161 cases of urticaria, 13 cases of facial or laryngeal edema and 13 cases of bronchospasm (4).

Palkowitsch et al. analyzed the safety and diagnostic image quality of Ultravist in a large non-interventional observational study of European and Asian patients (IMAGE Study) in 44,835 patients showing an overall ADR rate of 2.8% including 243 patients (0.54%) suffering from urticaria, erythema, and/or rash (5).

The very first study on AEs and hypersensitivity reactions (HSRs) after Ultravist administration in children and elderly has been carried out back in 1990 (7). More recently, also Dillman et al. focused on pediatric patients. They reported acute allergic-like reactions to Ultravist in 20 (0.18%) of the patients (6).

All author teams noted above concluded that AEs and ADRs, including hypersensitivity reactions, are rare.

A retrospective analysis on a large database bears the potential of answering the question if hypersensitivity reactions are different in different age groups.

Thus, the study aims to describe the risk of hypersensitivity reactions of Ultravist in the specific age groups of children (≤19 years of age) and elderly (≥60 years) compared to middle-aged adults (20-

59 years). It is suggested that children and elderly patients might experience lower rates of these reactions (7) due to either a developing (children) (6) or weakening (elderly) immune system. This new aspect has not thoroughly been investigated yet and Bayer possesses the data and the capacities to elucidate these questions.

8. Research questions and objectives

8.1 Primary objective

1. To describe the risk of hypersensitivity reactions to Ultravist in children (≤ 19 years of age) and elderly patients (20-59 years) compared to middle-age adults (≥ 60 years)

8.2 Secondary objective(s)

2. To describe the profile of HSRs in the three age groups
3. To describe the general reported ADR profile in the three age groups

9. Research methods

9.1 Study design

The study will be an observational, exploratory, nested case-control study based on integrated pooled database of four company sponsored non-interventional studies with iopromide (Ultravist). A total of around 152,233 records of patients will be analyzed. All studies have been published.

9.2 Setting

In this integrated analysis, the data of four company sponsored non-interventional studies with iopromide (Ultravist) in contrast-enhanced X-ray examination have been pooled. This pool consists of studies 'PMS I'(3), 'IMAGE'(5), 'TRUST'(8), 'Ultravist in CT'(9). All studies were all sponsored by Bayer or Schering. They comprise all available prospective observational studies with primary data collection performed with Ultravist.

These are:

- 'PMS I' was conducted in contrast-enhanced X-ray examination between June 1999 and November 2003 in 27 countries in Europe, Africa and Asia and comprised 74,717 patients of which 2,172 were children and 32,103 were elderly patients (3).
- 'IMAGE' consists of 44,835 patients with contrast-enhanced X-ray examination and was conducted in 21 European and Asian countries from February 2008 to September 2009, 1,451 patients were children, and 15,654 were elderly patients (5).
- 'TRUST' assessed the safety and tolerability of Ultravist in patients undergoing cardiac catheterization. It was conducted from August 2010 to September 2011 in China and included 17,513 patients of which 12 were children and 8,918 were elderly patients (8).

- 'Ultravist in CT' was performed with focus on contrast-enhanced CT examination between November 2006 and December 2008 and included 15,168 patients in Germany, Iran, Romania and Saudi Arabia. A total of 417 patients were children, 7,453 were elderly patients (9).

The total data pool consists of 152,233 patients, but may be further reduced due to missing values.

Table 1 shows the number of patients observed in the 4 studies.

Table 1: Number of patients potentially included in the analysis

Study	Countries	Study Duration	Patients	Ref.
PMS I	27 countries in Europe, US, Africa and Asia	6/1999 – 11/2003	74,717	(3)
IMAGE	21 countries in Europe & Asia	2/2008 - 11/2009	44,835	(5)
TRUST	China	8/2010- 11/2011	17,513	(8)
Ultravist in CT	Germany, Iran, Romania, Saudi Arabia	11/2006 – 12/2008	15,168	(9)
			152,233	

N.B. This data was already used for the UVIA-Project, that analyzed the impact of the administration route (intra-venous vs. intra-arterial) on hypersensitivity reactions (10).

9.2.1 Study population

The study population consists of patients who received a contrast enhanced X-ray based examination with Ultravist for various clinical reasons

9.2.2 Study time frame

All 4 observational studies were finalized and reported. Results and report are expected in QII 2021. No additional data will be collected.

9.2.3 Selection criteria

We included patients of all age groups which were referred to a iodine-based contrast-enhanced procedure of any body part. Patients with missing age, sex or who did not receive Ultravist 300 or 370 were excluded.

9.2.4 Representativeness

The current study utilizes data collected as a part of clinical practice across 37 countries and including Europe (mostly Germany and Spain), Asia (mostly China and South Korea) and USA.

Patients of all ages, both sexes, multiple ethnicities and across various health conditions/indications are represented in this pooled database. While the data might not represent a worldwide population precisely, the data cover broad range of regions and should be representative of those geographical areas.

9.3 Variables

There are a number of variables, which were collected during conduct of the trials and which might be relevant for our study. More specifically, the study will be utilizing information on age, sex, race, geographical region, iopromide concentration, iodine dose, history of hypersensitivity reactions, concomitant disease, premedication, indication and mode of injection.
Concomitant disease information coded with different terms across the four studies will be harmonized by mapping (see section 9.6). The outcome of interest is the record of at least one hypersensitivity reaction per patient (yes/no), which was documented in the observational studies.

9.3.1 Exposure definition

The integrated analysis will evaluate those patients who have received iopromide (iodine concentrations of 300 mg/mL or 370 mg/mL). The investigators were asked to comply with the local package insert. During the study period there were no major relevant label changes in any country affecting the study population (age, indications) or dosing. The main risk factor of interest is age defined by the following age groups: ≤19 years old - children; 20-59 years old - middle age adults; ≥60 years old – elderly. Age was originally recorded based on patient's records.

9.3.2 Outcomes definition

For the nested case-control analysis, cases and controls are defined as follows:

Cases (based on MedDRA version 21.0): Patients with any typical and unequivocal hypersensitivity reaction: anaphylactoid shock, angioedema, asthma, bronchospasm, conjunctivitis, cough, dysphagia, dyspnea, edema mucosal, erythema/exanthema/rash, hoarseness, lacrimation, laryngeal/pharyngeal/face edema, laryngeal/pharyngeal spasm, nasal stuffiness, pruritus/itching, respiratory arrest, rhinitis, sneezing, stridor, swelling (eyes/face), throat irritation, tongue edema, urticaria/hives/blisters, wheezing.

Control group: Patients without reported AEs.

Additionally, adverse events classified as ADRs will be descriptively presented.

9.3.3 Covariate definition

In this study covariates of interest are:

- patient characteristics (sex, race, geographic region)
- concomitant diseases (risk factors)
- pre-treatment (corticosteroids, H1/H2 blocker)
- dose and concentration of iodine
- route of administration

9.4 Data sources

The study will be conducted by pooling data of four company sponsored non-interventional studies with iopromide (see section 9.2).

9.5 Study size

About 139,000 records of patients are expected for evaluation, including approx. 4,000 children and 63,000 elderly patients. The sample size is determined by the available data from the four studies that will be analyzed.

In the previous pooled analysis of four non-interventional studies with Ultravist (10) the incidence of HSR was approximately 0.6%. Using this result as the assumption for this integrated analysis, the 95% confidence interval in the entire pool of about 139,000 patients is approximately [0.56%; 0.64%].

9.6 Data management

Taking into account that Bayer already is in possession of a pool containing information on all patients and variables of interest for the current research question, the study will use a pool prepared in 2018 for analysis (10).
During set up of this pool, coding of adverse events was updated to MedDRA version 21.0. It also used several data anonymization measures, such as: generating new patient numbers based on random numbers, eliminating patient initials, keeping only year of birth instead of full date of birth, removing device IDs and free text variables from adverse events description etc.

Full information on the setup of the pool as well as information on the data anonymization techniques used is given in Data Management Report from the original pooling activities for analysis (10).

(9)

9.7 Data analysis

Statistical analyses will be of exploratory nature only. No confirmatory hypothesis tests will be performed. In case that statistical test is performed, p-values will be interpreted as a metric for uncertainty. No adjustment for multiplicity will be done.

All variables will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by sample statistics (i.e. mean, standard deviation, minimum, median, quantiles and maximum). Continuous variables will be described by absolute value and as change from baseline, if applicable. Results will be presented by age groups specified earlier in the document.

The analysis population will consist of all patients of the study pool which received an injection (intra-arterial or intra-venous) with iopromide of the iodine concentrations of 300 mg/mL or 370 mg/mL at the discretion of the radiologist and have their age and sex recorded. A disposition table will be prepared to describe the number of patients which were not valid for analysis.

Records which contain missing data in variables needed for the analysis will be excluded. No imputation will be done.

All statistical details including calculated variables and proposed format and content of tables, listings and figures will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before the analysis starts.

9.7.1 Analysis of population characteristics

All background data such as subject demographics, specific concomitant diseases (risk factors), pre-medication, examination region, type of examination and indication for the application of iopromide will be described with summary statistics.

Concentration of iopromide will be summarized and total dose of iopromide applied will be calculated for each patient (ml and g iodine).

9.7.2 Analysis for the primary objective

Cases of hypersensitivity reactions will be identified following a preset case definition. Controls are patients without any AE after the contrast administration. The risk factor is defined as being either ≤19 years old or ≥60 years old compared to 20-59 years old group.

An unadjusted odds ratio with 95 % CI of the risk of hypersensitivity reactions for the children and elderly age groups compared to middle age group will be calculated in the case-control analysis. At the next step, the logistic regression will be further adjusted for potential confounders (e.g. sex, history of allergy, premedication etc.) in forward selection manner. The list of potential confounders will be based on the previous publication (10) and will be specified in SAP.

A covariate is considered important when its effect, represented by a descriptive p-value, is below 0.1. Subsequently, the covariates identified in the age-adjusted regression models will be brought together in a multivariate logistic regression model in order to identify the individual effect on the occurrence of hypersensitivity reactions. Potential confounding will be corrected at the analysis stage so no matching on confounders will be performed..

9.7.3 Analysis for the secondary objectives

HSR profile will be summarized with frequency tables by defined earlier age groups.

ADR profile will be summarized with frequency tables by defined earlier age groups.

9.8 Quality control

As no additional data will be captured the data quality relies on the source data of the integrated observational studies. The data in these studies were captured by paper or electronic CRFs. No checks for multiple documented patients will be done, because multiple documentation is unlikely given the different years and regions where the studies were conducted.

9.9 Limitations of the research methods

This is an integrated analysis on pooled data from four non-controlled, multi-center, observational cohort studies. The four studies were conducted in different years and in different countries and geographic regions all over the world. Nearly 45% of the pooled patients were enrolled in Europe, a further group of again 45% of the observed patients is from China. Geographical and cultural differences in the reporting of adverse events are possible.

Since the observation time of the patients in the observational studies used in this analysis was usually the time the patients spent in the radiology unit, late-onset hypersensitivity reactions occurring hours or days after injection are not captured.

There remains a possibility of unobserved confounding factors and hence a potential of bias due to unobserved confounding.

9.10 Other aspects

No other aspects need to be addressed.

10. Protection of human subjects

The data involved in the UV Age study may involve special categories of personal data according to Art. 9 General Data Protection Regulation (Regulation (EU) 2016/679) (GDPR).

The UV Age study will investigate the safety profile of Ultravist. As such, it supports ensuring high standards of quality and safety of health care and of medicinal products. Accordingly, the processing of the data in the context of the UV Age study should be based on Art. 9(2)(i) GDPR and on Section 22(1)(1c) of the German Act to Adapt Data Protection Law to Regulation (EU) 2016/679 and to Implement Directive (EU) 2016/680 (DSAnpUG-EU).

Furthermore, the UV Age study is a research study and aims at answering scientific questions. The processing is necessary for scientific purposes and, therefore, can also be justified based on Art.

9(2)(j) GDPR in connection with Section 27 DSAnpUG-EU. Additional safeguards will be applied as described under section 9.6.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. Reports of adverse events/reactions will be summarized in the study report (European Medicines Agency 2012).

12. Plans for disseminating and communicating study results

Study results will be presented in a study report following the STROBE checklist. The study results are intended to be published in an international peer-reviewed journal, e.g. Acta Radiologica, Clinical Radiology or European Journal of Radiology.

13. References

1. Krause W MH, Kollenkirchen U, Heimann G. Physicochemical Parameters of X-Ray Contrast Media. Invest Radiol. 1994;29(1):72-80.

2. Goldstein HA JG, Wiggins JR. New Clinical Trial Experience with Iopromide. Invest Radiol. 1994;29(Supplement 2):208-10.

3. Kopp AF, Mortele KJ, Cho YD, Palkowitsch P, Bettmann MA, Claussen CD. Prevalence of acute reactions to iopromide: postmarketing surveillance study of 74,717 patients. Acta Radiol. 2008;49(8):902-11.

4. Mortele KJ, Oliva MR, Ondategui S, Ros PR, Silverman SG. Universal use of nonionic iodinated contrast medium for CT: evaluation of safety in a large urban teaching hospital. AJR Am J Roentgenol. 2005;184(1):31-4.

5. Palkowitsch P, Lengsfeld P, Stauch K, Heinsohn C, Kwon ST, Zhang SX, et al. Safety and diagnostic image quality of iopromide: results of a large non-interventional observational study of European and Asian patients (IMAGE). Acta Radiol. 2012;53(2):179-86.

6. Dillman JR, Strouse PJ, Ellis JH, Cohan RH, Jan SC. Incidence and severity of acute allergic-like reactions to i.v. nonionic iodinated contrast material in children. AJR Am J Roentgenol. 2007;188(6):1643-7.

7. Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K. Adverse reactions to ionic and nonionic contrast media. A report from the Japanese Committee on the Safety of Contrast Media. Radiology. 1990;175(3):621-8.

8. Chen JY, Liu Y, Zhou YL, Tan N, Zhang B, Chen PY, et al. Safety and tolerability of iopromide in patients undergoing cardiac catheterization: real-world multicenter experience with 17,513 patients from the TRUST trial. Int J Cardiovasc Imaging. 2015;31(7):1281-91.

9. Palkowitsch PK, Bostelmann S, Lengsfeld P. Safety and tolerability of iopromide intravascular use: a pooled analysis of three non-interventional studies in 132,012 patients. Acta Radiol. 2014;55(6):707-14.

10. Endrikat J, Michel A, Kolbach R, Lengsfeld P, Vogtlander K. Risk of Hypersensitivity Reactions to Iopromide After Intra-Arterial Versus Intravenous Administration: A Nested Case-Control Analysis of 133,331 Patients. Invest Radiol. 2020;55(1):38-44.

14. Annex

Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	**Final version and date (if available)***
SAP (*tbd)*	Not yet available

* Draft versions are indicated by <draft> in brackets and date. "tbd" indicates documents that are not available at the time of protocol creation, but will be issued at a later stage

Annex 2: ENCePP checklist for post-authorization safety study (PASS) protocols

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

Study title: Safety profile of Ultravist in children and elderly (UV Age)

Study reference number: 21494

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	X	☐	☐	6
1.1.2 End of data collection[2]	X	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	X	
1.1.4 Interim progress report(s)	☐	☐	X	
1.1.5 Registration in the EU PAS register	X	☐	☐	6
1.1.6 Final report of study results.	X	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	7
2.1.2 The objective(s) of the study?	X	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	X	☐	☐	7 7
2.1.4 Which hypothesis (-es) is (are) to be tested?	X	☐	☐	7
2.1.5 If applicable, that there is no *a priori* hypothesis?				

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	X	☐	☐	7
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	X	☐	☐	7
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	X	☐	☐	7
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	7
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	X	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	X	☐	☐	10
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	X	☐	☐	8
4.2.2 Age and sex?	☐	☐	X	
4.2.3 Country of origin?	X	☐	☐	8
4.2.4 Disease/indication?	☐	☐	X	
4.2.5 Duration of follow-up?	☐	☐	X	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	8

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	X	☐	☐	7/8

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	X	
5.3 Is exposure categorised according to time windows? (e.g. current user, former user, non-use)	☐	☐	X	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)			X	
5.5 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☐	☐	X	
5.6 Is (are) (an) appropriate comparator(s) identified?				

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Page Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	X	☐	☐	7/11
6.2 Does the protocol describe how the outcomes are defined and measured?	X	☐	☐	7/12
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	12
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	X	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	X	☐	☐	12
7.2 Does the protocol address selection bias? (e.g. healthy user bias/adherer bias)	x			12
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	X	☐	☐	12

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	X	☐	☐	12

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Page Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	X	☐	☐	12
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	X	☐	☐	12
9.1.3 Covariates and other characteristics	X	☐	☐	9/10
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	12
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	12
9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	X	☐	☐	9/10
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	X	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	X	☐	☐	11/12
9.3.3 Covariates and other characteristics?	☐	☐	X	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number**
10.1 Are the statistical methods and the reason for their choice described?	X	☐	☐	10/11
10.2 Is study size and/or statistical precision estimated?				
10.3 Are descriptive analyses included?	X	☐	☐	10/11
10.4 Are stratified analyses included?	☐	☐	X	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number**
10.5 Does the plan describe methods for adjusting for confounding?	X	☐	☐	11
10.6 Does the plan describe methods for analytic control of outcome misclassification?				
10.7 Does the plan describe methods for handling missing data?	☐	☐	X	
10.8 Are relevant sensitivity analyses described?	☐	☐	X	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	12
11.2 Are methods of quality assurance described?	X	☐	☐	12
11.3 Is there a system in place for independent review of study results?	☐	☐	X	

Comments:

DMR would provide information on section 11.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☐	☐	X	
12.1.2 Information bias?	☐	☐	X	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☐	X	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	X	☐	☐	12

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☐	☐	X	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
13.3 Have data protection requirements been described?	X	☐	☐	12

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☐	☐	X	9

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	X	☐	☐	16
15.2 Are plans described for disseminating study results externally, including publication?	X	☐	☐	16

Comments:

Name of the main author of the protocol: PPD

Date: / /

Signature: _____

Annex 4: Signature pages

Signature Page – OS Conduct Responsible

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Name: PPD

Date, Signature:_____, _____

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Name: PPD

Date, Signature:_____, _____

Signature Page - OS Medical Expert

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page - OS Statistician

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page - OS Epidemiologist

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page - MAH contact person (Regulatory Affairs)

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____

Signature Page - OS Safety Lead

Title	Safety profile of Ultravist in children and elderly (UV Age Study)
Protocol version and date	v 1.0 / 21 Sep 2020
IMPACT study number	21494
Study type / Study phase	Observational, Phase IV PASS YES Joint PASS: NO
EU PAS register number	<Study not yet registered>
Medicinal product / Active substance	Ultravist / iopromide
Study Initiator and Funder	Bayer AG

The undersigned confirms that s/he agrees that the study will be conducted under the conditions described in the protocol.

Print Name: PPD

Date, Signature:_____, _____