Document Type:	Study Protocol
Official Title:	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
NCT Number:	NCT02959827
Document Date:	11 Oct 2016

Observational PASS

Title	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
Protocol version identifier	1.0
Date of last version of protocol	11 Oct 2016
EU PAS register number	Not registered
IMPACT number	19185
Phase	N/A
Active substance	N/A
Medicinal product	Iodinated contrast agents, e.g. iopromide
Product reference	NA
Procedure number	NA
Marketing authorization holder(s)	N/A
Joint Pass	No
Research question and objectives	This study will estimate the incidence of hypothyroidism in a pediatric population of children under age 4, based on data from the US-based Kaiser Permanente Northern California database, who were exposed to iodinated contrast agent through having a diagnostic procedure.
Country(-ies) of study	United States
Author	Susan Jick Director: Boston Collaborative Drug Surveillance Program PPD PPD USA

Marketing authorization holder *(table below mandatory for PASS studies)*

Marketing authorization holder(s)	*Bayer AG*

MAH contact person	PPD PPD *Bayer Pharma* PPD *Germany*

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

1. Table of Contents

2. List of abbreviations

BCDSP	Boston Collaborative Drug Surveillance Program
BU	Boston University
CI	Confidence Interval
CPT	Current Procedural Terminology
DMP	Data Management Plan
DRG	Diagnosis-Related Group
FDA	Food and Drug Administration
FFS	Fee-For-Service
GCP	Good Clinical Practice
HCPCS	Healthcare common procedure coding system
HMO	Health Maintenance Organization
HR	Hazard Ratio
ICD	International Classification of Diseases
IRB	Institutional Review Board
IT	Information Technology
KPNC	Kaiser Permanente Northern California
N/A	Not Applicable
NDC	National Drug Code
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
US	United States
WHO DD	World Health Organization Drug Dictionary

3. Responsible parties

BCDSP/BU:

Susan Jick DSc Director: Boston Collaborative Drug Surveillance Program; Professor of Epidemiology, Boston University School of Public Health

Kaiser Permanente Northern California:

Monique Hedderson PhD: Research scientist Kaiser Permanente Northern California Division of Research

Bayer:

PPD *Bayer Pharma,* PPD *Germany*

4. Abstract

Title: Study of Iodinated contrast agents and risk of hypothyroidism in young children in the United States

Rationale and background: While it is generally known and acknowledged that exposure to iodine contrast can interfere with thyroid function, little is known about the incidence of iodine-induced hypothyroidism in young children (under age 4).

Research question and objectives: The goal of this study is to estimate the incidence rate of detected hypothyroidism in a US-based general population of patients less than 4 years of age during years 2008 - 2015, who were exposed to an iodinated contrast agent.

Study design: This will be a retrospective cohort study.

Population: Patients less than age 4 in the US-based *Kaiser Permanente Northern California* data during years 2008 through 2015

Variables: Age, sex, calendar year, diagnostic procedure, comorbidities, treatments

Data sources: *Kaiser Permanente Northern California* database

Study size: There are millions patients under age 4 in the *Kaiser Permanente Northern California* database. From these data we expect to identify around 2300 pediatric patients who had a diagnostic procedure with an iodinated contrast agent.

Data analysis: We will estimate incidence rates of hypothyroidism in the 365 days post exposed procedure. We will also describe these patients according to characteristics, comorbidities, treatments, and diagnostic procedure received, as well as the time-relation between contrast exposure and hypothyroidism

Milestones: A preliminary report will be provided by December 2016 and a final report by 31 March, 2017

5. Amendments and updates

None

6. Milestones

Table 1 Milestones

Milestone	**Planned date**
Finalize study protocol	September, 2016
Obtain PPD approval	September 2016
Start of data collection	October 2016
End of data collection	November 2016
Preliminary report	22 December 2016
<Registration in the EU PAS register>	tbd
Final report of study results	31 March, 2017

7. Rationale and background

It is generally accepted that iodinated contrast agents can cause thyroid dysfunction because of the free iodide in the contrast solution. While a typical dose of 100 ml of contrast agent with an iodine concentration of 300 mg iodine/ml contains 30 g of bound iodine, the same solution also contains unbound or free iodine. Typical values of free iodide present in contrast material are CCI [redacted]. The actual amount of free iodide administered to a patient depends on the total dose, concentration and time between production of contrast agent and use.[1,2]

Excessive free iodide may inhibit thyroid hormone synthesis, causing hypothyroidism through an acute Wolff-Chaikoff effect. Normal thyroid hormone synthesis typically resumes after the acute Wolff-Chaikoff effect is corrected. Because neonates have immature thyroid tissue, they are especially susceptible to the Wolff-Chaikoff effect.[1,2] Since it is known that thyroid hormones are essential for the development of newborn and infants, hypothyroidism may pose a serious threat to a child's physical and mental development if left untreated. Hypothyroidism can affect both newborns and older children and can lead to delayed growth, overweight, enlargement of the thyroid gland, among other symptoms. In very young children prolonged hypothyroidism can lead to development delay. [3,4]

The incidence of hypothyroidism after exposure to iodinated contrast agents is unknown in this patient population. In a literature review by Ahmet et al.[1] nine studies were analyzed examining the effects of iodinated i.v. contrast media on thyroid function of neonates. Overall 8.3% of the term infants and 18.3% of the premature infants developed hypothyroidism after iodinated contrast media exposure; suggesting that preterm infants have an increased risk of hypothyroid compared to term infants. The authors noted that all studies were highly affected by bias. A retrospective database-study in a mainly adult patient population reported that iodinated contrast media exposure was associated with incident hyperthyroidism (odds ratio [OR], 1.98; 95% CI, 1.08-3.60), while no statistically significant association with incident hypothyroidism was observed (OR, 1.58; 95% CI, 0.95-2.62) (Rhee et al, Arch Int Med, 2012). In secondary analyses

an association with incident overt hypothyroidism was described. Due to its design, the study could not report incidence estimates of hypothyroidism following contrast exposure.

In general, hypothyroidism in children can have a wide variety of different etiologies including Hashimoto thyroiditis, some chromosomal disorders (Down Syndrome, Turner Syndrome), late-onset congenital hypothyroidism, as well as central hypothyroidism caused by pathologies in the pituitary gland or hypothalamus (Counts D et al. , 2009). Acquired childhood hypothyroidism, a result of decreased thyroid production caused by a failure in the hypothalamus and pituitary, has multiple causes including irradiation, drug exposures, iodine deficiency, neurosurgery, head trauma, tumors, or thyroid hormone resistance.[3,4] Drugs such as thionamides, lithium, amiodarone, interferon, and anticonvulsants are known to suppress thyroid function or interfere with thyroid synthesis.

We plan to estimate, in a large health maintenance organization (HMO) in Northern California, the rate of detected hypothyroidism in young children (age less than 4 years) exposed to an iodinated contrast agent.

8. Research questions and objectives

8.1 Primary objective

The goal of this study is to estimate the incidence rate of hypothyroidism, detected in routine clinical practice, in a US-based general population of patients less than 4 years of age during years 2008 - 2015, in the 365 days post exposure to an iodinated contrast agent. .
Hypothyroidism cases will be categorized into “probable iodine-induced hypothyroidism” and “possible alternative etiology” after medical records review.

8.2 Secondary objective(s)

The secondary objective(s) in this study is/are:

- To describe children who have procedures with iodinated contrast agents
- To describe the baseline characteristics of hypothyroidism cases and of the rest of the cohort as well as the time-relation between iodine contrast exposure and diagnosis of hypothyroidism, using descriptive statistics. This will be done for all hypothyroidism cases and separately for the “probable iodine induced” category and the “possible alternative etiology” category. In the “probable iodine induced” category we will further

ascertain the duration of the hypothyroidism episode.

9. Research methods

9.1 Study design

This will be a retrospective cohort study to describe patient characteristics and incidence of hypothyroidism in a pediatric population of children up to 365 days after a diagnostic scan with iodinated contrast agent. The study will be based on secondary data collection only.

9.2 Setting

This study will be conducted using data from the Kaiser Permanente Northern California (KPNC) database, a large US-based HMO database.

9.2.1 Study time frame

We will identify all patients in the KPNC database who were under age 4 during the years 2008 through 2015.

9.2.2 Selection criteria

We will identify all patients who were in the KPNC database and who were under age 4 at some time during the years 2008 through 2015.

9.2.3 Study population

The study population will be all patients who were under the age of 4 at some time during the years 2008 to 2015 in the US- based KPNC database who had a procedure with iodinated contrast agent. A preliminary search of the data identified around 2300 people under age 4 who had a procedure with iodinated contrast, by searching CPT and HCPCS codes. We will also require that all children in the study were members of KPNC for at least 3 months before the iodinated contrast exposure, except where the child is under 3 months of age at time of initial exposure, and 2 weeks after the exposure. From this population we will exclude all children who had a diagnosis of hypothyroid any time prior to the iodine contrast exposure. We will also exclude those with lab values for low thyroid (TSH > 5 mU/L for children) any time before the

exposure, and those with thyroid replacement therapy, Hashimoto thyroiditis, or congenital hypothyroidism any time prior to the exposure.

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9.3 Variables

9.3.1 Baseline characteristics

- Demographics characteristics (age, sex, year of procedure)
- Clinical characteristics (comorbidities, type of radiological examination, bodyweight, height, head-circumference, laboratory values (TSH, T3. T4 anti-thyroid antibodies, if available), and co-medications.

9.3.2 Exposure

Exposure will be identified through CPT codes for procedures that include iodinated contrast agent. The date the procedure was coded will be considered the date of exposure. The majority of these will be CT scans with contrast. We will also identify young children who had a left heart catheterization including cardio-angiography, ventriculography, and coronary angiography. Each child will be followed for up to 365 days after a qualifying exposure (the exposure window).

There will be no differentiation according to any specific brand of contrast agents, considering that there is general agreement that iodine induced hypothyroidism is considered a class-effect of all iodinated contrast agents and not restricted to specific agents

9.3.3 Outcome measures

Potential cases of hypothyroidism will be defined by:

- A coded diagnosis of hypothyroidism and/or
- A thyroid function tests indicating hypothyroidism and/or
- New use of thyroid replacement therapy

Cases of hypothyroid will be identified using ICD 9 DM codes, lab values and NDC codes. See appendix for code lists. From the exposed population we will identify all children who have a diagnosis of hypothyroidism in the 365 days after iodine contrast exposure. We will also identify those with lab values for low thyroid (TSH > 5.0 mU/L) or receipt of thyroid

replacement therapy in the 365 days post exposure. All children who meet any of these criteria will be considered potential cases of hypothyroidism. We will review the electronic record of each child considered to be a potential case to confirm that they did not have hypothyroidism prior to exposure to the iodine contrast agent. We will also look for codes that support the presence of the hypothyroid condition. For example if a child receives more than one prescription for thyroid replacement, or has multiple labs with high TSH levels, or multiple codes for hypothyroidism these will be considered likely cases. We will then obtain original clinical notes to validate the diagnosis, by searching for evidence of pre-existing thyroid conditions. Specifically will look for a positive diagnosis of hypothyroid, lab results, repeated lab tests, notes of other medications associated with lowered thyroid (see appendix 3 for list of drugs), and of Hashimoto thyroiditis, radiation, surgical procedures (see appendix 3 for list of procedures), and congenital forms of hypothyroid.

After review of their electronic medical record, detected cases will be classified into:

- Probable iodine-induced hypothyroidism: no other cause than the previous iodine contrast medium exposure could be identified
- Possible alternative etiology: Known other diseases (e.g. Hashimoto thyroiditis) or treatments (e.g. radiotherapy, drug treatments such as TK inhibitors, interferons, amiodarone and others) which may cause hypothyroidism
- Not a hypothyroidism case: No evidence of hypothyroidism in the patient's medical record, e.g. coding error

Estimated incidence rates will be calculated for all hypothyroidism cases together, and separate for "possible iodine induced hypothyroidism" and "possible alternative etiology."

9.4 Data sources

KPNC is an integrated health care delivery system providing health care to over 3.8 million members with 3,300 physicians, 32 outpatient clinics and 17 hospitals. Analysis of U.S. census data demonstrates that KPNC members are representative of the population living in the served geographic area.[5,6] KPNC maintains medical information on each patient through a computerized

EHR database called "Health Connect" since 2007. Therefore, we have access to high quality clinical data.

Admitting, Discharge and Transfer (ADT) System. A complete database on all hospitalizations at any KPNC hospital since 1971 is maintained with data that are highly comparable to the UB-92 forms (required of all hospitals in California and most other States), and contains a principal and up to 12 secondary discharge diagnoses and codes for up to seven procedures for each hospitalization. Admitting and discharge diagnoses and procedures are coded according to the International Classification of Disease, 9th revision (ICD-9).The accuracy of principal discharge diagnoses obtained from Kaiser Permanente databases has been verified in other studies.[5,6]

The Laboratory Utilization and Reporting System (LURS) is a clinical database that captures all laboratory tests and results performed at the Kaiser Permanente of Northern California regional laboratory since 1991. In 1995, LURS incorporated all hospital-based laboratories of Northern California. Providers use this system to order tests, obtain results and share them with patients. Thus, data in LURS are of higher quality than a chart review study could achieve (since chart review involves small rates of reviewer and transcription error). LURS contains patient name, medical record number, test name (each test has a unique code), date, and result. Essentially all thyroid tests ordered are available in the LURS database.

Outpatient Service Clinical Record (OSCR), a computerized database, will be a source to identify outpatient diagnosis of thyroid disorders.

The database contains a unique identifier for all information on all drugs issued to patients, all hospitalizations, captured with ICD-9 coding, outpatient diagnoses and laboratory tests and result. KPNC membership is stable and more than 97% of members have 5 or more years of membership.

9.5 Study Size

Around 2300 children exposed to iodinated contrast agent among all pediatric patients.

9.6 Data management

Data management will be conducted at KPNC where a data set of all children under age 4 will be created. From this database children exposed to iodinated contrast will be identified and followed for a year to detect hypothyroidism. Researchers at KPNC in collaboration with BU researchers will review electronic records to ensure data validity. All primary data will be held at KPNC. Further details can be found in the DMP.

9.7 Data analysis

Incidence density rates will be calculated using person-time of follow up. Baseline characteristics of the cases with hypothyroidism and of the rest of the cohort as well as the time-relation between iodine contrast exposure and diagnosis of hypothyroidism will be described using descriptive statistics. This will be done for all hypothyroidism cases and separately for the "probable iodine induced" category and the "possible alternative etiology" category. In the "probable iodine induced" category we will further ascertain the duration of the hypothyroidism episode.

If sample size and number of hypothyroidism cases allows, joint associations between possible risk factors and hypothyroidism will be examined in a multivariate statistical model (e.g. age, sex, bodyweight, type of procedure)

CCI [redacted]

9.8 Quality control

At the BCDSP/BU epidemiologists will work closely with our KPNC collaborators to ensure correct clinical definitions and data integrity. All analyses will be performed by trained epidemiologists familiar with large electronic health databases. We have procedures for checking data to be sure that the data have been correctly identified and classified. That is, we will check the characteristics of the study population to be sure they meet the study criteria by reviewing a random sample of electronic case records ("profiles"). We will create cross tabulations to describe the characteristics (including age, sex, comorbidities) of the study population and compare the results to the limited available epidemiology literature of hypothyroidism in young children and exposure to iodine in US youth. We will do data checks to confirm that person time was correctly calculated, and we will review the full electronic patient record to validate cases of

hypothyroidism and we will also abstract information from the patients complete medical records to validate all cases.

9.9 Limitations of the research methods

There is access to original clinical records in the KPNC database, thus validation will be possible. However we may miss some children who had procedure using iodinated contrast if the procedures were not coded properly. It is also possible that some children will have undiagnosed hypothyroidism. These will also be missed in this study.

Although most members enroll through their employers, many are members of KPNC through MediCal (a low-income health insurance plan). Analysis of U.S. census data demonstrates that KPNC members are representative of the general population with regard to ethnicity and education and differ only slightly with regard to income, we tend to underrepresent the very rich and the very poor. Members are remarkably similar to the general population in terms of employment status, marital status, screening practices, and prevalence of medical conditions, when compared with population-based data from the California Behavioral Risk Factor Surveillance System.

9.10 Other aspects

None noted

10. Protection of human subjects

Data will be derived from a large de-identified database (KPNC) and the study will go through the PPD review process to ensure protection of all patients involved.

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

Results will be provided to Bayer Pharma AG in a preliminary report no later than March 2017.

Study results will be published following guidelines of the International Committee of Medical Journal Editors (ICMJE, 2013), and communication in appropriate scientific venues will be considered.

When reporting results of this study, the appropriate STROBE checklist (STROBE, 2007) will be followed.

13. List of references

1. Ahmet A et al.: Hypothyroidism in neonates post-iodinated contrast media: a systematic review. Acta Pediatrica, 2009, pp 1568-1574
2. Rhee et al: Association between iodinated contrast media exposure and incident hyperthyroidism and hypothyroidism. Arch Intern Med. 2012;172(2):153-9
3. Counts D, Varma SK. Hypothyroidism in Children. Ped in review. 2009;30:251-57
4. Diaz A, Daiz EL, Hypothyroidism. Ped in review. 2014;35:336-47
5. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am.J.Public Health 1992;82(5):703-10
6. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001;285(18):2370-5

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	None	Sep 2016	

Annex 2. ENCePP checklist for study protocols (Revision 2, amended)

Adopted by the PPD on 14/01/2013; Doc.Ref. EMA/540136/2009

Study title:
Iodinated contrast agents and risk of hypothyroidism in young children in the United States

Study reference number:
TBD

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]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	6
1.1.4 Interim progress report(s)	☐	☐	☒	6
1.1.5 Registration in the EU PAS register	☐	☐	☒	6
1.1.6 Final report of study results.	☒	☐	☐	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	☒	☐	☐	

[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 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
management plan, an emerging safety issue)				
2.1.2 The objective(s) of the study?	☒	☐	☐	7-8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which formal hypothesis (-es) is (are) to be tested?				
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	
	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	13

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	9

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9
4.2.2 Age and sex?	☒	☐	☐	9
4.2.3 Country of origin?	☒	☐	☐	9
4.2.4 Disease/indication?	☒	☐	☐	10
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

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 categorising exposure)	☒	☐	☐	9
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)	☒	☐	☐	11
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	10
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the product?	☒	☐	☐	7
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	10-11
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	11

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	11
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	11

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.) 8.1.2 Endpoints? (e.g. clinical records, laboratory markers	☒	☐	☐	11 - 12

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	10
8.1.3 Covariates?	☒	☐	☐	10 - 11
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, product quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	10
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10 - 11
8.2.3 Covariates? (e.g. age, sex, clinical and product use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	11
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	10 + 24-25
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	10 + 24-25
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	12

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	12

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	13
10.3 Are descriptive analyses included?	☒	☐	☐	13
10.4 Are stratified analyses included?	☒	☐	☐	13
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a descriptive study so there are no issues of confounding.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	13
11.3 Are methods of quality assurance described?	☒	☐	☐	13
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	13,14
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Data are descriptive and missing data is not a concern.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐ ☐	☐ ☐	☒ ☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	12
12.3 Does the protocol address other limitations?	☒	☐	☐	14

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?	☒	☐	☐	14
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	TBD
13.3 Have data protection requirements been described?	☒	☐	☐	13

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?	☒	☐	☐	6

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)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: ___Susan Jick DSc

Date: 21/03/2016

Signature: _____

Annex 3. Additional information

Codes for procedures used to identify study patients exposed to iodinated contrast agents

Procedure codes	CPT and HCPCS	Data source
CT scans with contrast	70470, 70482, 70488, 70491, 70492, 70496, 70498, 71270, 71275, 72126, 72127, 72128, 72129, 72130, 72133, 72191, 72194, 73202, 73206, 73702, 73706, 74170, 74174, 74175,	KPNC data
Left heart catheterization	93452, 93453, 93454, 93455, 93456, 93457	
Ventriculography	93458, 93459, 93460, 93461	
Cardio/ Coronary angiography	93563, 93564, 93565, 93566	

Codes for used to identify study patients with hypothyroidism

Diagnosis, lab and treatment codes	ICD-9-CM and NDC	Data source
Hypothyroidism	244.9	244.
Hashimoto thyroiditis	245.2	
Congenital hypothyroidism	243	
HT due to iodine	244.2	
HT Due to irradiation therapy	244.1	
HT Due to surgery	244.0	
HT Due to specific cause	244.8	

HT Due to medication	244.3	
Thyroid replacement	Codes for thyrogen	
Lab values		

HT =Hypothyroidism

Codes used to identify medications and procedures associated with hypothyroidism

Drugs and procedures	**ICD-9-CM, CPT and NDC**	**Data source**
Irradiation to neck	92.2	KPNC data
Cranial irradiation		
Neurosurgery		
Craniopharyngioma tumors		
Down Syndrome		
Turner Syndrome		
Propylthiouracil		
Methimazole		
Carbimazole		
Lithium		
Carbemazepine		
Valproic acid		
Ethotoin		
Phenytoin		
Amiodarone		
Interferon		

Annex 4. Signature pages

Signature Page -Investigators

Title	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
Protocol version identifier	1.0
Date of last version of protocol	12 09 2016
IMPACT study number	19185
Study type	x☐ PASS non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	Not applicable
Marketing authorization holder(s)	Bayer
Function	Investigator
Name	Susan Jick
Title	Professor, Director
Address	Boston Collaborative Drug Surveillance Program Boston University School of Public Health PPD

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

Date, Signature: PPD _____

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?	☒	☐	☐	6

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)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: ___Susan Jick DSc

Date: 21/03/2016

Signature: PPD 10/12/16

Signature Page – PPD

Title	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
Protocol version identifier	1.0
Date of last version of protocol	Sep 2016
IMPACT study number	19185
Study type	X☐ PASS non PASS
EU PAS register number	*NA*
Active substance (medicinal product)	*NA*

Marketing authorization holder(s)	Bayer Pharma
Function	PPD
Name	PPD
Title	PPD
Address	Bayer Pharma AG
	PPD

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

Date, Signature: 25/10/16 , PPD

Signature Page –

PPD

Title	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
Protocol version identifier	1.0
Date of last version of protocol	Sep 2016
IMPACT study number	19185
Study type	X☐ PASS non PASS
EU PAS register number	N/A
Active substance (medicinal product)	N/A

Marketing authorization holder(s)	Bayer Pharma
Function	PPD
Name	PPD
Title	PPD
Address	Bayer Pharma AG
	PPD Germany

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

Date, Signature: Oct. 13, 2016, PPD

Title	Iodinated contrast agents and risk of hypothyroidism in young children in the United States
Protocol version identifier	1.0
Date of last version of protocol	12 09 2016
IMPACT study number	19185
Study type	X☐ PASS non PASS
EU PAS register number	Study not registered
Active substance (medicinal product)	Not applicable
Marketing authorization holder(s)	Bayer

Function	Investigator
Name	Monique Hedderson
Title	PhD
Address	*Kaiser Permanente Northern California Division of Research*

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

Date, Signature: 10/26/16, PPD