Post Authorization Safety Study (PASS) Information

Acronym/Title	Association between the Prevalence of cardiovascular risk factors and new use of testosterone
Protocol version and date	0.6, 22 January 2018
IMPACT study number	19547
Study type / Study phase	Observational ☒ PASS Joint PASS: ☐ YES ☒ NO
EU PAS register number	TBD
Active substance	Testosterone
Medicinal product	[redacted]
Product referenc	N/A
Procedure number	N/A
Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	The objective is to investigate if established cardiovascular risk factors predict the initiation of testosterone use.
Country(-ies) of study	United Kingdom
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	[redacted]
MAH contact person	[redacted]

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

BMI	Body mass index
CPRD	Clinical Practice Research Datalink
EMA	European Medicine Agency
FDA	Food and Drug Administration
ENCePP	European Network of Centers in Pharmacoepidemiology and Pharmacovigilance
GP	General practitioner
HES	Hospital Episodes Statistics
HSCIC	Health and Social Care Information Centre
ICD	International Classification of Diseases
ISAC	Independent Scientific Advisory Committee
MHRA	Medicines and Healthcare products Regulatory Agency
N/A	Not applicable
NHS	National Health Service
NIHR	National Institute for Health Research
ONS	Office for National Statistics
OPCS-4	Office of Population Censuses and Surveys: Classification of Interventions and Procedures, version 4
OR	Odds ratio
OS	Observational Study
OXMIS	Oxford Medical Information System
PAS	Post-authorization study
PASS	Post-authorization safety study
PI	Principal investigator
PRAC	Pharmacovigilance Risk Assessment Committee
RCT	Randomized controlled trial
SAP	Statistical analysis plan
UK	United Kingdom

3. Responsible parties

3.1 Study initiator and funder

Role: OS Conduct Responsible
Name:
E-mail:

Role: OS Safety Lead
Name:

Role: OS Medical Expert
Name:

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

3.2 Collaborator(s)

Role: OS Epidemiologist, Author
Name:

Role: OS Statistician
Name:

Administrative changes of responsible persons will be documented by updating the respective lists, but do not require formal protocol amendments.

4. Abstract

Acronym/Title	Association between the prevalence of cardiovascular risk factors and new use of testosterone
Protocol version and date	0.6, 22 January 2018
IMPACT study number	19547
Study type / Study phase	Observational
Author	[redacted]
Rationale and background	Testosterone undecanoate [redacted]) is indicated for treatment of male testosterone deficiency (pathological or functional hypogonadism). Pathological hypogonadism occurs in approximately 3% of the male population. In contrast, functional hypogonadism is highly prevalent (up to 50%) in men with obesity and/or type 2 diabetes, both considered chronic diseases and risk factors for cardiovascular diseases. (1) Functional hypogonadism can occur at all ages and is not related to advancing age but rather to the presence of comorbidities, in particular chronic conditions as obesity (BMI $\geq$30 kg/m^2) and type 2 diabetes mellitus.
Research question and objectives	The objective is to investigate if established cardiovascular risk factors predict the initiation of testosterone use.
Study design	This will be a matched case-control study.
Population	The source population is the subset of male patients in the Clinical Practice Research Datalink (CPRD) that has been linked to the Hospital Episodes Statistics (HES) database (CPRD-HES). Cases will be defined by first testosterone use between 1st January 2001 and 31st March 2016 (study period). The date of the GP consultation associated with the first testosterone prescription will be designated as the index day. All cases will be required to be over 18 years on the index day, to have contributed for at least 2 years to the CPRD-HES link and to

	have no history of testosterone before the index day. For each case, up to five controls will be drawn from the source population. Controls will be matched on exact year of birth, history of pathological hypogonadism (primary or secondary) and GP consultation ±30 days of the index day of the respective case. The index day of a control will be the day of the closest GP visit to the index day (i.e. the calendar day) of the corresponding case. Controls are required to have contributed for at least 2 years to the CPRD-HES link before their index day and to have no history of testosterone use on or before the index day.
Variables	Cases will be ascertained using specific product and Read medical codes indicating use of testosterone. Pathological hypogonadism and risk factors for cardiovascular events will be defined using (1) hospital-based information consisting of specific ICD-10 codes for hospital discharge diagnoses and specific OPCS-4 codes for in-hospital procedures, and (2) primary care information comprising Read medical codes for diagnoses, symptoms and procedures, and prescriptions issued by GPs. Further details will be provided in the Statistical Analysis Plan (SAP).
Data sources	All data will be obtained from the United Kingdom CPRD with additional data from the HES.
Study size	A previous CPRD study identified over 4600 male patients aged 18 or older with first-ever testosterone use between January 2001 and February 2016 and two years of history in CPRD-HES. The matched control group is expected to consist of up to 23,000 patients as it is intended to select up to five controls for each new testosterone user.
Data analysis	Descriptive statistics of the demographic and baseline clinical characteristics on the index day will be presented for cases and their matched controls. This will include lifestyle factors, proportion with pathological hypogonadism (primary or secondary), frequent symptoms associated with functional hypogonadism, comorbidities, comedications and cardiovascular risk factors. Crude and adjusted odds ratios (OR) with 95% confidence intervals of the association between cardiovascular risk factors and initiation of testosterone therapy will be estimated using conditional logistic regression for matched case-control data. Results will be stratified by history of pathological

	hypogonadism.
Milestones	Provision of a first draft study report is planned to be submitted to Bayer approximately 3 months after approval of the study protocol by Bayer AG and by CPRD's Independent Scientific Advisory Committee (ISAC). Provision of the final study report is expected to be submitted to Bayer approximately 3 weeks after receipt of Bayer's final comments on the draft study report. It is assumed that Bayer AG has online access to CPRD, that access to CPRD GOLD is granted via Bayer AG, and that there is a third party agreement between Bayer AG and the Institute for Epidemiology, Statistics and Informatics GmbH in place for CPRD to provide HES linkage datasets.

5. Amendments

None.

6. Milestones

Table 1 presents planned milestones for the project.

It is assumed that Bayer AG has online access to CPRD, that access to CPRD GOLD is granted via Bayer AG, and that there is a third party agreement between Bayer AG and the Institute for Epidemiology, Statistics and Informatics GmbH in place for CPRD to provide HES linkage datasets.

Table 1: Milestones

Milestone	**Planned date**
Start of data collection	Within one month after Bayer and ISAC approval of study protocol
End of data collection	Within two months after Bayer approval of study protocol
Provision of draft study report	Within three months after Bayer approval of study protocol
Final report of study results	Three weeks after receipt of final Bayercomments on draft study report

7. Rationale and background

Testosterone undecanoate ([redacted]) is indicated for treatment of male testosterone deficiency (pathological or functional hypogonadism). Pathological hypogonadism occurs in approximately 3% of the male population. In contrast, functional hypogonadism is highly prevalent (up to 50%) in men with obesity and/or type 2 diabetes, both considered chronic diseases and risk factors for cardiovascular diseases.

There are concerns regarding the safety of long-term testosterone therapy, e.g. cardiovascular endpoints and prostate cancer. An ongoing debate about cardiovascular safety was triggered by one RCT,(2) two retrospective epidemiological database analyses,(3, 4) and one meta-analysis (5) leading to safety investigations by FDA and EMA (PRAC procedure). Only three RCTs with a duration of 3 years are published to date on the use of testosterone patch in relatively healthy, slightly overweight men over 65 years with low-normal testosterone; (6-9) use of short-acting testosterone injections in relatively healthy, overweight men aged 65 years and above with low testosterone (n=46);(10, 11) and use of testosterone gel in relatively healthy, overweight men aged 60 years and above with low or low-normal testosterone (n=155).(12)

Since 2010, four papers were published suggesting an increased cardiovascular risk in middle-aged to elderly men receiving testosterone therapy.(3-5, 12) These papers triggered safety assessments by EMA and FDA. Both agencies could not detect conclusive evidence for an increased cardiovascular risk, however, the FDA decided to add a warning in the label of testosterone-containing products. In contrast to those 4 papers, numerous publications reported that testosterone therapy reduces all-cause and cardiovascular mortality and morbidity.(13-17)

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) review did not confirm an increase in heart problems with testosterone medicines but decided that "The cardiovascular safety of testosterone medicines will continue to be monitored and the findings of ongoing studies will be reflected in the next regular benefit-risk assessments when available."(18)

Testosterone therapy is considered standard treatment in men with functional hypogonadism. Functional hypogonadism can occur at all ages and is not solely related to advancing age but rather to the presence of comorbidities, in particular chronic conditions as obesity (BMI ≥30 kg/m^2) and type 2 diabetes mellitus.(1, 19)

We will investigate if testosterone is preferentially given to patients at higher risk of cardiovascular events. If this is the case, then observational studies may be prone to selection bias resulting in overestimation of the cardiovascular risk associated with testosterone when compared to a healthier population not taking testosterone.

8. Research questions and objectives

8.1 Primary objective

The objective is to investigate if established cardiovascular risk factors predict the initiation of testosterone use.

8.2 Secondary

N/A

9. Research methods

9.1 Study design

This will be a matched case-control study.

9.2 Setting

9.2.1 Study time frame

1 January 2001 to 31 March 2016 (study period).

9.2.2 Selection criteria

9.2.2.1 Cases selection

9.2.2.1.1 Inclusion criteria

All male individuals in the source population with a first testosterone use during the study period will be included as cases. The date of the GP consultation associated with the first testosterone prescription will be designated as the index day.

9.2.2.1.2 Exclusion criteria

Patients of less than 18 years on the index day, with less than 2-year contribution to the CPRD-HES link before the index day, or with use of testosterone before the study period will be excluded from the group of cases.

9.2.2.2 Controls selection

For each case, controls will be drawn among people in the source population. Controls will be matched on exact year of birth, history of pathological hypogonadism (primary or secondary) and GP consultation ±30 days of the index day of the respective case. The index day of the control will be the day of the closest GP visit to the index day (i.e. the calendar day) of the corresponding case. Controls are required to have contributed for at least 2 years to the CPRD-HES link before their index day and to have no history of testosterone use on or before the index day.

For each case, all patients in the source population that fulfill all matching criteria will be identified (control candidates).

The matching procedure for a given case will be applied as follows:

1. all patients predisposed to initiate testosterone of the same age (as the respective case) will be identified (control candidates);
2. control candidates will then be restricted to those with a GP visit ±30 days to the calendar day of the case's GP visit with the initial testosterone prescription;
3. the index day of the remaining control candidates will be defined as the calendar day of the closest GP visit to the respective case's index day;
4. control candidates with a history of testosterone use before or on the respective index date will be dropped from the list of control candidates;
5. control candidates will be further restricted to match the case's history of pathological hypogonadism on their index day;
6. from the remaining list of control candidates that fulfill all matching criteria, 5 patients will be randomly selected. If less than 5 candidates are available then all control candidates will be kept;
7. cases without any control candidate will be dropped from the list of cases but unlikely given the size of the source population, the frequency of the matching factors and the expected proportion of testosterone initiators of less than 0.3% in the source population;
8. controls are selected from the source population with replacement.

For cases with less than five control candidates all control candidates will be kept. Cases without any control candidate will be dropped from the group of cases and not be included in the regression analysis. We expect that no control candidates will be found for a small number of cases only. The study objective is to investigate if established cardiovascular risk factors predict the initiation of testosterone use, cannot be investigated among cases without controls. Nevertheless, the baseline characteristics of those patients will be presented separately. A patient can be selected as a control for more than one case, as can patients with subsequent testosterone initiation after their index day.

9.2.3 Study population

9.2.3.1 Source

The source population is the subset of male patients in the Clinical Practice Research Datalink (CPRD) that have been linked to the Hospital Episodes Statistics (HES) database (CPRD-HES).

9.2.3.2 Sampling strategy

Cases will be sampled from all individuals in the CPRD with a first-time testosterone prescription during the study period. Controls will be matched with replacement on each case's index day as specified in 9.2.2.2.

9.2.3.3 Representativeness

CPRD is considered representative of the demographic distribution of the UK.

The CPRD is an ongoing primary care database of anonymised medical records from general practitioners, with coverage of over 11.3 million patients from 674 practices in the UK. With 4.4 million active (alive, currently registered) patients meeting quality criteria, approximately 6.9% of the UK population are included.

When compared with the UK census in 2011, CPRD patients are broadly representative of the UK population in terms of age and sex. Patients are also comparable to the UK census in terms of ethnicity, and comparable to the Health Survey for England for body mass index distribution in most patient subgroups. However, the CPRD may not be representative of all practices in the UK based on geography and size. (20)

9.3 Variables

9.3.1 Baseline characteristics

Demographic characteristics include age, BMI, smoking status and socioeconomic class. While the information on age and gender is complete in CPRD, the completeness of other demographic characteristics is about 95%. Clinical characteristics of the cases and controls consisting of comorbidities and medication use will be assessed as of the index day.

Comorbidities will consist of pathological hypogonadism (primary or secondary), history of stroke/transient ischaemic attack, atrial fibrillation, myocardial infarction, ischaemic heart disease, heart failure, hypertension, hypercholesterolemia, diabetes, other Charlson score components, and comorbidities, which sometimes lead to empirical testosterone treatment (i.e. sexual dysfunction, osteoporosis, infertility, hot flushes, loss of appetite, and a group of symptoms comprising tiredness, lethargy and depression).

The following medications will be assessed: lipid-lowering drugs, antihypertensive medications, positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, drugs affecting the renin-angiotensin system, nitrates, calcium-channel blockers, potassium-channel activators, anticoagulants and antiplatelet drugs.

9.3.2 Exposure

The exposure of interest is the presence of the following cardiovascular risk factors: history of stroke/transient ischaemic attack, atrial fibrillation, myocardial infarction, ischaemic heart disease, heart failure, hypertension, diabetes, hypercholesterolemia, high BMI, current- and ex-smoking, deprived socioeconomic class, lipid-lowering drugs, antihypertensive medication, positive inotropic drugs, diuretics, anti-arrhythmic drugs, beta-adrenoceptor blocking drugs, drugs affecting the renin-angiotensin system, nitrates, calcium-channel blockers, potassium-channel activators and anticoagulant or antiplatelet drugs.

9.3.3 Outcome measures

The study outcome is the initiation of testosterone therapy. Testosterone therapy will be identified from prescriptions and specific Read medical codes.

9.4 Data sources

Data for this study will be obtained from the United Kingdom CPRD. The CPRD is jointly funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA). CPRD is based on primary care and includes information on demographics, lifestyle factors, consultations, medical history, symptoms and diagnoses recorded with Read medical codes, prescribed primary care drugs, and laboratory data (tests and results). CPRD also includes socio-economic information provided by quintiles of the Index of Multiple Deprivation, a measure of material deprivation calculated using census data and linked to area of residence.

HES is based on hospital visits and includes dates of hospital admission and discharge, primary and other reasons for treatment recorded with International Classification of Diseases, Tenth Revision (ICD-10), and surgical operations and procedures performed during hospital stay recorded with the 4th revision of the classification of surgical operations and procedures of the Office of Population Censuses and Surveys (OPCS-4). Linkage with HES is needed to increase the completeness and validity of cardiovascular risk factors and pathological hypogonadism in the entire study population (cases and controls).

A subset of English practices (currently 75%, representing 58% of all UK CPRD practices) have consented to participate in the CPRD linkage scheme and have provided patient-level information. Patient-level data from consenting practices are linked via a trusted third party (NHS Digital, formerly known as the Health and Social Care Information Centre) to other existing data sources and include Hospital Episode Statistics (hospitalisation data), Office for National Statistics (mortality data including causes of death), Index of Multiple Deprivation and Townsend scores (deprivation data) and disease registries including the National Cancer Intelligence Network. (20).

Linkage of CPRD data with HES only happens if a practice explicitly gives permission for this in addition to supplying anonymised primary care data. Such linkages do require the use of direct patient identifiers in order to establish a confident match of the same individual. On behalf of CPRD this linkage is done by NHS-Digital, formerly known as the Health and Social Care Information Centre (HSCIC), an approved Trusted Third Party. Only the HSCIC receives the identifiers and provides CPRD the “pseudonym ID”. The pseudonym ID is common to the linked data sets and indicates that the records belong to the same person – but without revealing who that person is.

9.5 Study size

A previous CPRD study identified over 4600 male patients aged 18 or older with first-ever testosterone use between January 2001 and February 2016 and two years of history in CPRD/HES. The matched control group is expected to consist of up to 23,000 patients as it is intended to select up to five controls for each new testosterone user.

The ability to detect statistically significant predictors of testosterone initiation will depend on the prevalence of each predicting factor to be investigated and on the magnitude of the true odds ratio. The prevalence of potential predictors of testosterone initiation in the controls is supposed to range between 1% (e.g. positive inotropic drugs) and 30% (e.g. ex-smokers).

The relationship between the prevalence of a potential predictor in the control group and the minimum magnitude of the respective odds ratio estimate to become statistically significant with 80% power and significance level of 5% is detailed in the table below:

Prevalence of covariate in controls	Estimated odds ratio with statistically significant results
1%	>1.5
5%	>1.3
10%	>1.2
20%	>1.2
30%	>1.1

For example if 10% of controls are obese, then obesity will only be a statistically significant predictor of testosterone initiation if the estimated odds ratio is greater than 1.2 with 80% power and 5% significance level.

9.6 Data management

The study data will be collected by CPRD. Data retrieval and preparation of data for online access to the principal investigator (PI) is done by CPRD. The validity of the data and the quality of the data management is the responsibility of CPRD, see section 9.8.

9.7 Data analysis

Descriptive statistics of the demographic and baseline clinical characteristics on the index day will be presented for matched and unmatched cases and for the respective controls. This will include lifestyle factors (i.e. body mass index, smoking and alcohol status), proportion with pathological hypogonadism (primary or secondary), comorbidities, comedications and cardiovascular risk factors.

Crude and adjusted odds ratios (OR) with 95% confidence intervals of the association between cardiovascular risk factors and initiation of testosterone therapy will be estimated using conditional logistic regression for matched case-control data. Adjusted ORs will be derived from the model including the cardiovascular risk factors listed in '9.3.2 Exposure' as potential predictors of testosterone initiation and all variables listed in '9.3.1 Baseline characteristics' as potential confounders. No selection procedure for covariates will be used. Analyses will also be stratified by history of pathological hypogonadism. A sensitivity analysis will be conducted assessing the relationship between cardiovascular risk factors and initiation of testosterone therapy separately for the two time periods 2001 to 2014 and 2015 to 2016 as the testosterone prescribing behavior might be influenced by the publication of the FDA warning letter in 2015.

The following clinical characteristics will be assessed within the year prior to the index day: hot flushes, loss of appetite, and the group of symptoms comprising tiredness, lethargy and depression. All other covariates will be assessed during the entire period prior to the index day.

Further details will be provided in the Statistical Analysis Plan (SAP). All statistical procedures will be performed using the Stata MP Version 14.2 (StataCorp LP).

The study protocol in the format required by the Independent Scientific Advisory Committee (ISAC) for CPRD research needs ISAC approval for CPRD to provide HES and IMD linkage datasets.

9.8 Quality control

Official documentation on the CPRD states the following information on data collection, quality assurance procedures and data processing:(21)

9.8.1 Data collection

Data are collected from selected volunteering practices using the Vision Clinical System software provided by In Practice Systems Ltd. On acceptance as a CPRD contributor, an initial data collection of all available historic electronic medical record data is taken from the practice computer. Because of the size of this data collection, these data are saved to media and sent to the CPRD Group through a tracked postal service. Subsequent data collections are performed on an incremental basis approximately every four weeks. As these files are much smaller they are transmitted electronically to the CPRD via the secure NHS intranet. The data are verified for integrity and completeness before further processing. If a collection fails these checks a recollection is requested.

The software required to carry out the data collection process is an integral part of the Vision Practice software system.

The MHRA has a contract with In Practice Systems Ltd. to ensure that CPRD data collection are uninterrupted in the event of upgrades to the Vision software.

The collection software identifies the practice using the In Practice Systems Ltd. User Number. The collection software does not collect any other practice identifiers. The collection software also encrypts the identity numbers of GPs and other practice staff who enter data into their system. At the time of registration, the practice computer allocates a unique identifier to each patient. This identifier is used by the practice system to allocate later data to the same patient file. The collection software does not collect the data fields of the patients which contain strong identifiers (e.g. title, name, address, postcode, telephone number, NHS number, etc.).

As an additional precaution, the patient identifier and practice number are encrypted for a second time prior to being made available to researchers via the CPRD data warehouse.

9.8.2 Quality assurance procedures

Data quality assurance processes are undertaken as part of the data processing (stage 7) on the compiled data in the CPRD resource. The aim of the quality assurance is to provide guidance to users to enable the most appropriate use of the data, ensuring that the data used for research are of the highest quality and exclude patient populations inappropriate for use in research. This is achieved through a 7 stage process that targets individual patients, and data associated with practices as a whole. Patients are labelled as ‘acceptable’ for use in research by a process that identifies and excludes patients with non-contiguous follow up or patients with poor data recording that raises suspicion as to the validity of that patient’s record. Patient data are checked, for the following issues:

• An empty or invalid first registration date

• Absence of a record for a year of birth

• A first registration date prior to their birth year

• A transferred out reason with no transferred out date

• A transferred out date with no transferred out reason

• A transferred out date prior to their first registration date

• A transferred out date prior to their current registration date

• A current registration date prior to their first registration date

• A current registration date prior to their birth year

• A gender other than Female/Male/Indeterminate

• An age of greater than 115 at end of follow-up

• Recorded health care episodes in years prior to birth year

• Registration status of temporary patients

• Invalid or missing event dates for all recorded events

If any of these conditions are true then the patient is labelled unacceptable, and is not recommended for use in research. The overall quality of data in practices is mediated by use of an 'up-to-standard' date, which is deemed as the date at which data in the practice are considered to have continuous high quality data fit for use in research. This is mediated by an analysis on the total data in the practice which is refreshed every time a new collection for a practice is processed into the database. It is based on two central concepts: assurance of continuity in data recording, and avoidance of use of data for which transferred out and dead patients have been removed.

The continuity of recording is assessed by undertaking gap analysis. This works by identifying periods where there exist 5 consecutive 7-day windows where the number of events in each window falls below 30% of the median number of events for this practice. This being a significant gap, the gap date is set to the earliest date after which there is no significant gap.

The assessment of the presence or absence of transferred out and dead patients from the data are undertaken by looking at mortality in the practice. The gaps between deaths in the practice are assessed, with the maximum allowable gap being set to a value representing seven times the expected gap between deaths based on the UK mortality rate, given the practice size, plus a static period of 31 days. The large safety margin built in is set to account for both geographical and seasonal variation in death rates, and also because the removal of transferred out patients and dead patients from practice data at a certain point in time would result in a death rate of close to zero prior to the date or removal of old patients. This 'removal date' is set to the earliest date in the list of death dates where the maximum gap is not exceeded. The up-to-standard date is set to the earlier of the gap date and the removal date.

9.8.3 Data processing

Collection loading takes collections received by CPRD and runs a series of checks including checking for mandatory files, and establishing continuity of records relative to previous collections. It logs details of this and other aspects of the collection to an administrative database and presents the data ready for processing.

Processing takes the collection data available and manipulates it such that it is output into the finished ASCII text files. The resulting data are passed through a build process which makes the monthly database ready to be queried and analysed for research purposes. The overall processing is archived through a sequence of stages:

Stage 1 identifies if there is a viable collection to process. This involves the checking for the presence of key and optional data files, and also a check of the structure within each of the files to ensure that it is correct. The collection is then archived.

Stage 2 strips out the fields that are not required in the processing and the resulting files are archived for use for merging in subsequent collections.

Stage 3 combines data from all data collections in order to enable the identification and appropriate processing of updated records. The latest version of each updated record is retained as the current version.

Stage 4 removes the deleted records from all the data by referencing a special mandatory collection file which contains logs of records deleted since the last collection.

Stage 5 retains only Read coded data in the database, no data are lost but records coded by OXMIS in previous versions of CPRD are now coded by Read codes.

Stage 6 encodes the text data in the data files replacing them with numeric lookups, reducing the size of the database, and rendering it easier to manipulate computationally.

Stage 7 is where the quality assurance analysis takes place resulting in patient acceptability criteria and 'up-to-standard dates' (see Quality assurance procedures section). Additionally, feedback reports are generated from the data here, which is provided to GPs to identify problems and encourage better and more standardized recording practices.

Stage 8 organises the data into a consistent column and row order, additionally, it sorts by patient identifier to enable query tools to index the data without having to further reorder the data.

Database creation or build is undertaken on a monthly basis by taking a snapshot of the fully processed data and organizes it to provide the required data structures to enable the data extraction tools. All lookups and dictionaries are updated and made available in a consistent manner, and checks on record counts are undertaken to ensure data integrity.

9.9 Limitations of the research methods

As in all observational studies unmeasured confounding or hidden bias might exist.

Data on inpatient drug use and hospital discharge medication are very limited or not available in CPRD. Thus, information on in-hospital testosterone use will be missed. If testosterone was given in the in-hospital setting only and not recorded by the GP, then some controls may have a history of testosterone use or be current testosterone users on their index day and thus would bias the odds ratio estimate towards the 1.

Diagnosis of an existing cardiovascular risk factor (e.g. asymptomatic AF) may be more likely in patients with a condition leading to initiation of testosterone use than in patients without these conditions. This would lead to an overestimation of the respective odds ratio estimates. To reduce this problem, we have matched on GP visit to assure contact with the GP in matched controls ±30 days to the index day of the respective case.

Information on testosterone levels is hardly available in CPRD. Therefore adjustment for testosterone levels is not feasible with this database. If low testosterone levels would be related to both, cardiovascular risk factors (e.g. obesity) and the initiation of testosterone use, then odds ratios for testosterone initiation in the respective cardiovascular risk factors would be overestimated. To address this issue, we will stratify odds ratio estimation by history of pathological hypogonadism.

Furthermore, information on the indication for testosterone treatment is not available if not coded as a hospital discharge diagnosis in hospital or by the GP. Study results could be confounded if the recording of the indication for testosterone use (e.g. pathological hypogonadism or sexual dysfunction) is differential among cases and controls.

9.10 Other aspects

N/A

10. Protection of human subjects

The CPRD Group has obtained blanket ethics approval for observational studies undertaken using the CPRD. This means that for almost all CPRD studies there is no requirement for customers to seek their own ethics approval. Where a study involves some form of patient intervention it is likely that ethics approval will be required. In this scenario, the CPRD Group can use the benefit of its experience to provide support in obtaining necessary approvals.

All studies resulting in publication require the prior approval of the Independent Scientific Advisory Committee (ISAC). This Committee is constituted to ensure studies undertaken using the CPRD are of an appropriately high scientific standard.

The ISAC application process changed on the 1st of July 2015. After this date the new ISAC application form must be submitted. In the interest of transparency, from the 1st July 2015 CPRD makes the key details of approved ISAC protocols publically available. The details published will include the names of the researchers and their organisations involved in the studies, the purpose of the research and the ISAC decision regarding the protocols. Details of approved studies are made available 3 months after the commencement of the projects in order to give researchers time to make progress on their projects before the study details are released. (22)

This will be a retrospective analysis of data in the CPRD. Identification of individual patients will not be possible, and so there will be no risk to patients as a result of the study.

Personal identifiers of the datasets are not collected. CPRD uses methods of anonymisation at more than one point in the process when making data available for a research project. UK and European law controls all access and use of data. Researchers can only access key datasets via standard security systems including a passphrase which changes every 30 seconds. CPRD requires a certificate on the computers of authorized researchers. Physical security is ensured through a tier 3 data centre. Security measures are regularly reviewed and audited.

The CPRD software programmes used to extract information from GP systems do not collect identifiers such as name, NHS number, full date of birth, etc. as part of the research data extract – effectively anonymising the extracted data. In addition, researchers using CPRD never have access to any information that identifies patients, their doctors or the specific general practice. Researchers are also bound by legal contract not to behave in a way that would lead to the identification of individuals or practices. CPRD works with the Primary Care Research Network to encourage practices to contribute to the work of CPRD and information may be shared with them and the Clinical Research Network Coordinating Centre about the extent of a practice's involvement with CPRD. Before any linkage with other data sets can take place it has to be approved by the Ethics and Confidentiality Committee of the National Information Governance Board.

Linkage of CPRD data with HES only happens if a practice explicitly gives permission for this in addition to supplying anonymised primary care data. Such linkages do require the use of direct patient identifiers in order to establish a confident match of the same individual. On behalf of CPRD this linkage is done by an approved Trusted Third Party, the HSCIC, that receives the identifiers and not CPRD. The HSCIC provides CPRD with the "pseudonym ID" that is common to the linked data

sets and indicates that the records belong to the same person – but without revealing who that person is.

In accordance to CPRD policy, cells containing <5 events/patients will not be presented on the publication stage.

11. Management and reporting of adverse events/adverse reactions

Not applicable as per the EMA Guideline on Good Pharmacovigilance Practices (Module VI– Management and reporting of adverse reactions to medicinal products[Revision 1]), (23) for non-interventional study designs that are based on secondary use of data.

12. Plans for disseminating and communicating study results

The results of this observational study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses.

13. References

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Annex 1: List of stand-alone documents

Table 2: List of stand-alone documents

Document Name	Final version and date (if available)*
SAP	TBD

* 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

Not applicable

Annex 3: Additional information

Not applicable

Annex 4: Signature pages