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INVESTIGATION OF PSYCHIATRIC ADVERSE EVENTS FOLLOWING EXPOSURE TO LEVONORGESTREL CONTAINING INTRAUTERINE DEVICES

Data analysis plan of THIN electronic health record data

Roles

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Study aim

This study investigates whether levonorgestrel delivered by an intra-uterine device (LNG IUD) increases the risk of anxiety, panic attacks, sleep disorders and restlessness.

Data source

UK electronic primary care data contained within the THIN database.

Study design and selection criteria

Given the long term nature of the IUD exposure, a cohort study with time to first occurrence of a diagnosis related to the events of interest following insertion of the IUD will be conducted. A control arm consisting of women using IUDs not medicated with levonorgestrel (or other hormonal product) will provide a comparison. Age, factors associated with the outcome events and differences in indications between the LNG medicated and un-medicated IUDs will be taken into account. Matching on practice may help to balance some unknown social factors.

Eligible participants for the active arm of the study will include women fitted with an LNG IUD and with more than one year of prior data collection in THIN. A search over time prior to study entry will be made for codes indicative of previous use of such devices and women will be excluded the new IUD appears to be a replacement of a previous one. It should be noted that this is not a perfect process because the 5 year intended duration of protection means that codes may be very infrequently used. Identical exclusions, based on the same time periods, will be applied to treatment and comparator groups.

Comparator group

Although the signal under investigation relates specifically to IUDs containing LNG, in this study we investigate the hypothesis that the relevant adverse effects might be caused by systemic exposure to LNG and not related to any other component of the device. Hence a potential comparator group

is formed of women who are fitted with IUDs that do not contain LNG. Product codes for treatment and control groups are given in Annex A and overall annual counts of exposed women are shown in Annex E.

Assessment of continuous exposure

A new contraceptive episode, either treatment or control group, will be defined as starting with the issue date of a prescription for an IUD when no such prescription or indication of usage is found in the preceding full year. To assess continuity of exposure, Read codes for removal of IUDs will be searched and duration of exposure will be reported. Some work on the use of different methods of contraception has been previously done using the THIN dataset (Cea-Soriano et al) and will be reviewed.

Although Read codes exist related to insertion and removal of IUDs, scoping analysis suggests these may not be systematically used or necessarily associated with the correct date (see Annex G) and are hence not used in defining the study period.

Study start and end dates

The study will include women prescribed IUDs between 1 January 2000 and 31 December 2016. Women prescribed IUDs will be included with a minimum of one full year of observation time is available before the prescription date (cohort entry) and prior coding suggests that this is a first exposure to the type of IUD in the relevant arm of the study. Women must be recorded as formally enrolled with a THIN practice meeting the Acceptable Mortality Reporting (AMR) date before study entry. No other data quality measures will be required.

The time to censoring (cohort exit) will be the earliest of: end of exposure (up to five years from the prescription date), the point at which the patient leaves the practice or dies, or the date of last data collection for the practice. The proportion of patients dying should be small but will be reported as a check.

Primary comparison: LNG IUD vs. non-LNG IUD comparison

Analyses will be performed for time from prescription to first occurrence of:

- A Read code diagnosis or prescription indicating anxiety
- A Read code diagnosis indicating a panic attack
- A Read code diagnosis or prescription indicating sleep disturbance
- A Read code diagnosis indicating restlessness
- The first of any of the above Read code diagnoses (composite outcome)

Outcomes will be defined by Read codes or, for anxiety and sleep disturbance, by prescriptions of anxiolytics or sedative-hypnotics. As active anxiety at cohort entry may be associated with read codes reiterating the previous diagnosis, patients with previous anxiety symptoms or treated with anxiolytics at cohort entry will be excluded from the primary analysis. Similarly patients with prior symptoms of other outcomes or treated with sedatives-hypnotics will be excluded from the primary analysis of the relevant outcomes. However, in all cases, secondary analyses will examine the potential effects in the excluded groups. For each outcome, crude incidence of outcomes will be calculated for the treatment and control groups. A Cox proportional hazards regression model will be fitted estimating crude and adjusted hazard ratios with 95% confidence intervals. Adjustment will

be made for all baseline variables. No selection of confounders will be made unless the model fails to converge. The proportional hazards assumption will be checked.

The main comparisons will be LNG IUDs against non-LNG IUDs over the entire exposure period. An exposure period of up to five years from the start of treatment has been defined due to the duration of action of LNG containing IUDs. However, it is possible that natural variation in susceptibility (Renoux et al) or other mechanisms will lead to time variation in hazard ratios. Therefore analysis will also be performed evaluating risk with shorter durations of exposure at 6 months following cohort entry.

Baseline characteristics will be compared between LNG and non-LNG containing products including: age, history of menorrhagia, endometriosis, dysmenorrhea, premenstrual syndrome, peri-menopausal symptoms, recent history of childbirth, anaemia, smoking status, alcohol, deprivation, recorded history of any of the outcome events or of depression, co-prescribed medications (anxiolytics, antidepressants, benzodiazepines, antipsychotics, inhalers, oral contraceptives, tranexamic acid); and contraceptive treatment regimen within the previous year. Codes related to IUD treatment discontinuation and any potential problems with use of the IUDs during the study period will be compared between the treatment arms.

Sensitivity analyses and further investigation

1. The indication for treatment may vary by age (e.g. the indication for LND IUD in older women may relate to pre-menopausal symptoms). Sensitivity analysis will be conducted examining the effects of age at baseline.
2. The effects of treatment with the subgroup of women who gave birth within one year prior to the study will be examined.
3. Some Read codes relate to both depression and anxiety. For the primary analysis these will be excluded but sensitivity analysis will be carried out in which they are included.
4. Exclusion of women with unclear codes related to insertion or removal of IUDs. See Annex G. The forms of switching and the possibility and possible relationship to outcome events will be described.
5. Descriptive analyses will be performed of the associations between study outcome events and also between these events and depressive symptoms.

Assay sensitivity analysis

An association is already documented between depression and exposure to levonorgestrel and an analysis will be carried out to determine if this can be detected in this dataset. This will be carried out prior to the analyses of study outcomes and may be used to improve sensitivity if appropriate.

References

Lucía Cea Soriano, Mari-Ann Wallander , Susan W Andersson , Gema Requena , Luis A García-Rodríguez. Study of Long-Acting Reversible Contraceptive Use in a UK Primary Care Database: Validation of Methodology. *Eur J Contracept Reprod Health Care* 19 (1), 22-28. 2013.

Renoux C, Dell'Aniello S, Brenner B, Suissa S. Bias from depletion of susceptibles: the example of hormone replacement therapy and the risk of venous thromboembolism. *Pharmacoepidemiol Drug Saf.* 2017;26:554-560.

Code lists

Product codes for LNG and non-LNG IUDs are included in Annex A. Codes related to management of contraceptive devices are included in the Read dictionary and these may give indications about prior use of, removal of or problems with the device. These are included in Annex B.

BNF codes for other classes of contraceptive are included in Annex C. Read codes for events related to anxiety, panic attacks, sleep disorders and restlessness are listed in Annex D. Depression codes for the assay sensitivity analysis are also included.

Annex A Product Codes

Levonorgestrel IUDs

drugcode	bnfcode1	strength	units	atc	genericnameuc
50916978	07.03.02.03	52	mg	G02B A03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
75898978	07.03.02.03	13.5	mg	G02B A03	LEVONORGESTREL 13.5MG INTRAUTERINE DEVICE
75899978	07.03.02.03	13.5	mg	G02B A03	LEVONORGESTREL 13.5MG INTRAUTERINE DEVICE
91324998	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
91325998	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
92849979	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE
92851979	07.03.02.03	52	mg	G03A C03	LEVONORGESTREL 20MICROGRAMS/24HOURS INTRAUTERINE DEVICE

Other IUDs used as comparator group 1

drugcode	bnfcode1	atc	genericnameuc
58042979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
58043979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
58044979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59356979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59358979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59359979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
59360979	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
71058994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
80741994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83855994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83856994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83858994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
83859994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
84171994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
86053994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
87355979	00.00.00.00		INTRAUTERINE CONTRACEPTIVE DEVICE
87911994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
89797994	07.03.04.00	G02B A01	INTRAUTERINE CONTRACEPTIVE DEVICE
89798994	07.03.04.00	G02B A01	INTRAUTERINE CONTRACEPTIVE DEVICE
90662994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91073994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91074994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
91271994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
95678994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97021994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97339992	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97916994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
97917994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
98212994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
99235994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE
99880994	07.03.04.00	G02B A02	INTRAUTERINE CONTRACEPTIVE DEVICE

Annex B. Medical codes related to intrauterine contraceptive devices

615J.00	UNSUCCESSFUL INTRAUTERINE CONTRACEPTIVE DEVICE INSERTION
615K.00	INTRAUTERINE CONTRACEPTIVE DEVICE ANNUAL REVIEW
615L.00	INTRAUTERINE CONTRACEPTIVE DEVICE 6 WEEK CHECK
615M.00	INTRAUTERINE CONTRACEPTIVE DEVICE ANNUAL REVIEW BY TELEPHONE
615N.00	INTRAUTERINE CONTRACEPTIVE DEVICE FIT BY ANOTHER GP PRACTICE
615Q.00	INTRAUTERINE CONTRACEPTIVE DEVICE REMOVED BY OTHER HLTH PROVIDER
615R.00	INTRAUTERINE CONTRACEPTIVE DEVICE CHECKED BY OTHER HLTH PROVIDER
61R..00	INTRAUTERINE SYSTEM CONTRACEPTION
677S.00	COUNSELLING FOR INTRAUTERINE DEVICE
679K200	EDUCATION FOR INTRAUTERINE SYSTEM
7D1E400	REMOVAL INTRAUTERINE CONTRACEPTIVE DEVICE FROM POUCH OF DOUGLAS
7D1E411	REMOVAL OF CONTRACEPTIVE COIL FROM POUCH OF DOUGLAS
7E09.00	INTRAUTERINE CONTRACEPTIVE DEVICE PROCEDURE
7E09.11	COIL INTRAUTERINE CONTRACEPTIVE DEVICE PROCEDURE
7E09.12	INTRAUTERINE DEVICE PROCEDURE
7E09000	INTRODUCTION OF INTRAUTERINE CONTRACEPTIVE DEVICE
7E09011	FITTING OF INTRAUTERINE CONTRACEPTIVE DEVICE
7E09100	REPLACEMENT OF INTRAUTERINE CONTRACEPTIVE DEVICE
7E09111	CHANGE OF INTRAUTERINE CONTRACEPTIVE DEVICE
7E09200	REMOVAL OF INTRAUTERINE CONTRACEPTIVE DEVICE NEC
7E09300	REMOVAL OF DISPLACED INTRAUTERINE CONTRACEPTIVE DEVICE
7E09600	REPLACEMENT OF INTRAUTERINE SYSTEM
7E09700	INSERTION OF INTRAUTERINE SYSTEM
7E09800	REMOVAL OF INTRAUTERINE SYSTEM
7E09y00	OTHER SPECIFIED INTRAUTERINE CONTRACEPTIVE DEVICE
7E09z00	INTRAUTERINE CONTRACEPTIVE DEVICE PROCEDURE NOS
8CEF.00	INTRAUTERINE DEVICE CONTRACEPTION LEAFLET GIVEN
962..13	IUCD CONTRACEPTIVE CLAIM
962..14	IUD CONTRACEPTIVE CLAIM
962..15	IUD CONTRACEPTIVE CLAIM
98BA.00	GMS3 CLAIM - TEMPORARY CONTRACEPTIVE (IUCD) SIGNED
98BB.00	GMS3 CLAIM - TEMPORARY CONTRACEPTIVE (IUCD) SENT TO HA
98BC.00	GMS3 CLAIM - TEMPORARY CONTRACEPTIVE (IUCD) PAID
9KA..00	INTRA-UTERINE CONTRACEPTIVE DEVICE FITTING - ENH SERV ADMIN
9m6..00	INTRAUTERINE CONTRACEPTIVE DEVICE REMOVAL INVITATION
L2D..00	RETAINED INTRAUTERINE CONTRACEPTIVE DEVICE IN PREGNANCY
SP03200	MECHANICAL COMPLICATION OF INTRAUTERINE CONTRACEPTIVE DEVICE
SP03212	MECHANICAL COMPLICATION INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD)
SP03213	MECHANICAL COMPLICATION INTRAUTERINE CONTRACEPTIVE DEVICE (IUD)
SP03214	PERFORATION UTERUS DUE TO INTRAUTERINE CONTRACEPTIVE DEVICE (IUCD)
SP03215	PERFORATION UTERUS DUE TO INTRAUTERINE CONTRACEPTIVE DEVICE (IUD)
SP03216	BLEEDING DUE TO INTRAUTERINE CONTRACEPTIVE DEVICE
SP03900	UTERINE PERFORATION BY INTRAUTERINE CONTRACEPTIVE DEVICE
SP03A00	EXPULSION OF INTRAUTERINE CONTRACEPTIVE DEVICE
SP06C00	INFECTION ASSOCIATED WITH INTRAUTERINE CONTRACEPTIVE DEVICE
SP07R00	BLEEDING DUE TO INTRAUTERINE CONTRACEPTIVE DEVICE
SP07S00	RETAINED INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25100	[V]INTRAUTERINE CONTRACEPTIVE DEVICE INSERTION
ZV25112	[V]INTRAUTERINE CONTRACEPTIVE DEVICE INSERTION
ZV25113	[V]INTRAUTERINE CONTRACEPTIVE DEVICE INSERTION
ZV25414	[V]INTRAUTERINE CONTRACEPTIVE DEVICE CHECK
ZV25415	[V]REINSERTION OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25416	[V]REMOVAL OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25419	[V]INTRAUTERINE CONTRACEPTIVE DEVICE CHECK
ZV2541A	[V]REINSERTION OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV2541B	[V]REMOVAL OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25A00	[V]SURVEILLANCE OF (INTRAUTERINE) CONTRACEPTIVE DEVICE
ZV25D00	[V]REINSERTION OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25E00	[V]REMOVAL OF INTRAUTERINE CONTRACEPTIVE DEVICE
ZV25F00	[V]INTRAUTERINE CONTRACEPTIVE DEVICE CHECK
ZV45500	[V]INTRAUTERINE CONTRACEPTIVE DEVICE PRESENT
ZV45511	[V]INTRAUTERINE CONTRACEPTIVE DEVICE PRESENT
ZV45512	[V]INTRAUTERINE CONTRACEPTIVE DEVICE PRESENT

Annex C: BNF codes used for extraction of prescriptions of contraceptives

bnfcode1	DESCRIPTION	COUNT_of_drugcode
07.03.01.00	COMBINED HORMONAL CONTRACEPTIVES	123
07.03.02.01	ORAL PROGESTOGEN-ONLY CONTRACEPTIVES	24
07.03.02.02	PARENTERAL PROGESTOGEN-ONLY CONTRACEPTIVES	17
07.03.02.03	INTRA-UTERINE PROGESTOGEN-ONLY DEVICE	7
07.03.03.00	SPERMICIDAL CONTRACEPTIVES	38
07.03.04.00	CONTRACEPTIVE DEVICES	418
07.03.04.02	DIAPHRAGMS	7
07.03.04.03	CONTRACEPTIVE CAPS	2
07.03.05.00	EMERGENCY CONTRACEPTION	10

Annex D: Read Codes for Outcome Events

Code	UCName	Group
8G94.00	ANXIETY MANAGEMENT TRAINING	Anxiety
8HHp.00	REFERRAL FOR GUIDED SELF-HELP FOR ANXIETY	Anxiety
E2...00	NEUROTIC; PERSONALITY AND OTHER NONPSYCHOTIC DISORDERS	Anxiety
E20..00	NEUROTIC DISORDERS	Anxiety
E200.00	ANXIETY STATES	Anxiety
E200000	ANXIETY STATE UNSPECIFIED	Anxiety
E200200	GENERALISED ANXIETY DISORDER	Anxiety
E200300	ANXIETY WITH DEPRESSION	Anxiety
E200400	CHRONIC ANXIETY	Anxiety
E200500	RECURRENT ANXIETY	Anxiety
E200z00	ANXIETY STATE NOS	Anxiety
E201.00	HYSTERIA	Anxiety
E201000	HYSTERIA UNSPECIFIED	Anxiety
E201100	HYSTERICAL BLINDNESS	Anxiety
E201200	HYSTERICAL DEAFNESS	Anxiety
E201300	HYSTERICAL TREMOR	Anxiety
E201400	HYSTERICAL PARALYSIS	Anxiety
E201500	HYSTERICAL SEIZURES	Anxiety
E201511	FIT - HYSTERICAL	Anxiety
E201600	OTHER CONVERSION DISORDER	Anxiety
E201611	ASTASIA - ABASIA; HYSTERICAL	Anxiety
E201612	GLOBUS HYSTERICUS	Anxiety
E201700	HYSTERICAL AMNESIA	Anxiety
E201800	HYSTERICAL FUGUE	Anxiety
E201900	MULTIPLE PERSONALITY	Anxiety
E201A00	DISSOCIATIVE REACTION UNSPECIFIED	Anxiety
E201800	COMPENSATION NEUROSIS	Anxiety
E201z00	HYSTERIA NOS	Anxiety
E201z11	APHONIA - HYSTERICAL	Anxiety
E201z12	ATAXIA - HYSTERICAL	Anxiety
E201z13	GANSER'S SYNDROME - HYSTERICAL	Anxiety
E202.00	PHOBIC DISORDERS	Anxiety
E202.11	SOCIAL PHOBIC DISORDERS	Anxiety
E202.12	PHOBIC ANXIETY	Anxiety
E202000	PHOBIA UNSPECIFIED	Anxiety
E202300	SOCIAL PHOBIA; FEAR OF EATING IN PUBLIC	Anxiety
E202400	SOCIAL PHOBIA; FEAR OF PUBLIC SPEAKING	Anxiety
E202500	SOCIAL PHOBIA; FEAR OF PUBLIC WASHING	Anxiety
E202600	ACROPHOBIA	Anxiety
E202800	CLAUSTROPHOBIA	Anxiety
E202900	FEAR OF CROWDS	Anxiety
E202B00	CANCER PHOBIA	Anxiety
E202D00	FEAR OF DEATH	Anxiety
E202E00	FEAR OF PREGNANCY	Anxiety
E202z00	PHOBIC DISORDER NOS	Anxiety
E202z11	WEIGHT FIXATION	Anxiety
E203.00	OBSESSIVE-COMPULSIVE DISORDERS	Anxiety
E203.11	ANANCASTIC NEUROSIS	Anxiety
E203000	COMPULSIVE NEUROSIS	Anxiety
E203100	OBSSSIONAL NEUROSIS	Anxiety
E203z00	OBSESSIVE-COMPULSIVE DISORDER NOS	Anxiety
E205.00	NEURASTHENIA - NERVOUS DEBILITY	Anxiety
E205.11	NERVOUS EXHAUSTION	Anxiety
E205.12	TIRED ALL THE TIME	Anxiety
E206.00	DEPERSONALISATION SYNDROME	Anxiety
E207.00	HYPOCHONDRIASIS	Anxiety
E20y.00	OTHER NEUROTIC DISORDERS	Anxiety
E20y000	SOMATIZATION DISORDER	Anxiety
E20y011	BRIQUET'S DISORDER	Anxiety
E20y100	WRITER'S CRAMP NEUROSIS	Anxiety
E20y200	OTHER OCCUPATIONAL NEUROSIS	Anxiety
E20yz00	OTHER NEUROTIC DISORDER NOS	Anxiety
E20z.00	NEUROTIC DISORDER NOS	Anxiety
E20z.11	NERVOUS BREAKDOWN	Anxiety

E26..00	PHYSIOLOGICAL MALFUNCTION ARISING FROM MENTAL FACTORS	Anxiety
E260.00	PSYCHOGENIC MUSCULOSKELETAL SYMPTOMS	Anxiety
E260000	PSYCHOGENIC PARALYSIS	Anxiety
E260100	PSYCHOGENIC TORTICOLLIS	Anxiety
E260200	PSYCHOGENIC MUSCULOSKELETAL SYMPTOMS NOS	Anxiety
E261.00	PSYCHOGENIC RESPIRATORY SYMPTOMS	Anxiety
E261000	PSYCHOGENIC AIR HUNGER	Anxiety
E261100	PSYCHOGENIC COUGH	Anxiety
E261200	PSYCHOGENIC HICCOUGH	Anxiety
E261300	PSYCHOGENIC HYPERVENTILATION	Anxiety
E261400	PSYCHOGENIC YAWNING	Anxiety
E261500	PSYCHOGENIC APHONIA	Anxiety
E262.00	PSYCHOGENIC CARDIOVASCULAR SYMPTOMS	Anxiety
E262000	CARDIAC NEUROSIS	Anxiety
E262200	NEUROCIRCULATORY ASTHENIA	Anxiety
E262300	PSYCHOGENIC CARDIOVASCULAR DISORDER	Anxiety
E262z00	PSYCHOGENIC CARDIOVASCULAR SYMPTOM NOS	Anxiety
E263.00	PSYCHOGENIC SKIN SYMPTOMS	Anxiety
E263000	PSYCHOGENIC PRURITUS	Anxiety
E263z00	PSYCHOGENIC SKIN SYMPTOMS NOS	Anxiety
E264.00	PSYCHOGENIC GASTROINTESTINAL TRACT SYMPTOMS	Anxiety
E264.11	GLOBUS ABDOMINALIS	Anxiety
E264000	PSYCHOGENIC AEROPHAGY	Anxiety
E264200	CYCLICAL VOMITING - PSYCHOGENIC	Anxiety
E264300	PSYCHOGENIC DIARRHOEA	Anxiety
E264400	PSYCHOGENIC DYSPEPSIA	Anxiety
E264500	PSYCHOGENIC CONSTIPATION	Anxiety
E264z00	PSYCHOGENIC GASTROINTESTINAL TRACT SYMPTOM NOS	Anxiety
E265.00	PSYCHOGENIC GENITOURINARY TRACT SYMPTOMS	Anxiety
E265100	PSYCHOGENIC VAGINISMUS	Anxiety
E265200	PSYCHOGENIC DYSMENORRHEA	Anxiety
E265300	PSYCHOGENIC DYSURIA	Anxiety
E26y.00	OTHER PSYCHOGENIC MALFUNCTION	Anxiety
E26z.00	PSYCHOSOMATIC DISORDER NOS	Anxiety
E278.00	PSYCHALGIA	Anxiety
E278000	PSYCHOGENIC PAIN UNSPECIFIED	Anxiety
E278100	TENSION HEADACHE	Anxiety
E278111	MUSCULAR HEADACHE	Anxiety
E278200	PSYCHOGENIC BACKACHE	Anxiety
E278z00	PSYCHALGIA NOS	Anxiety
E28..00	ACUTE REACTION TO STRESS	Anxiety
E28..11	COMBAT FATIGUE	Anxiety
E281.00	ACUTE FUGUE STATE DUE TO ACUTE STRESS REACTION	Anxiety
E282.00	ACUTE STUPOR STATE DUE TO ACUTE STRESS REACTION	Anxiety
E283.00	OTHER ACUTE STRESS REACTIONS	Anxiety
E283000	ACUTE SITUATIONAL DISTURBANCE	Anxiety
E283100	ACUTE POSTTRAUMA STRESS STATE	Anxiety
E283z00	OTHER ACUTE STRESS REACTION NOS	Anxiety
E284.00	STRESS REACTION CAUSING MIXED DISTURBANCE OF EMOTION/CONDUCT	Anxiety
E28z.00	ACUTE STRESS REACTION NOS	Anxiety
E29..00	ADJUSTMENT REACTION	Anxiety
E292.00	ADJUSTMENT REACTION; PREDOMINANT DISTURBANCE OTHER EMOTIONS	Anxiety
E292000	SEPARATION ANXIETY DISORDER	Anxiety
E292400	ADJUSTMENT REACTION WITH ANXIOUS MOOD	Anxiety
E292y00	ADJUSTMENT REACTION WITH MIXED DISTURBANCE OF EMOTION	Anxiety
E292z00	ADJUSTMENT REACTION WITH DISTURBANCE OF OTHER EMOTION NOS	Anxiety
E293.00	ADJUSTMENT REACTION WITH PREDOMINANT DISTURBANCE OF CONDUCT	Anxiety
E293000	ADJUSTMENT REACTION WITH AGGRESSION	Anxiety
E293100	ADJUSTMENT REACTION WITH ANTISOCIAL BEHAVIOUR	Anxiety
E293200	ADJUSTMENT REACTION WITH DESTRUCTIVENESS	Anxiety
E294.00	ADJUSTMENT REACTION WITH DISTURBANCE EMOTION AND CONDUCT	Anxiety
E29y.00	OTHER ADJUSTMENT REACTIONS	Anxiety
E29y000	CONCENTRATION CAMP SYNDROME	Anxiety
E29y100	OTHER POST-TRAUMATIC STRESS DISORDER	Anxiety
E29y200	ADJUSTMENT REACTION WITH PHYSICAL SYMPTOMS	Anxiety
E29y300	ELECTIVE MUTISM DUE TO AN ADJUSTMENT REACTION	Anxiety
E29y500	OTHER ADJUSTMENT REACTION WITH WITHDRAWAL	Anxiety

E29yz00	OTHER ADJUSTMENT REACTIONS NOS	Anxiety
E29z.00	ADJUSTMENT REACTION NOS	Anxiety
E2D0.00	Disturbance of anxiety and fearfulness childhood/adolescent	Anxiety
E2y..00	OTHER SPECIFIED NEUROSES OR OTHER MENTAL DISORDERS	Anxiety
E2z..00	NEUROSES OR OTHER MENTAL DISORDER NOS	Anxiety
Eu05400	[X]ORGANIC ANXIETY DISORDER	Anxiety
Eu34114	[X]PERSISTANT ANXIETY DEPRESSION	Anxiety
Eu4..00	[X]NEUROTIC; STRESS - RELATED AND SOMOFORM DISORDERS	Anxiety
Eu40.00	[X]PHOBIC ANXIETY DISORDERS	Anxiety
Eu40000	[X]AGORAPHOBIA	Anxiety
Eu40011	[X]AGORAPHOBIA WITHOUT HISTORY OF PANIC DISORDER	Anxiety
Eu40100	[X]SOCIAL PHOBIAS	Anxiety
Eu40112	[X]SOCIAL NEUROSIS	Anxiety
Eu40200	[X]SPECIFIC (ISOLATED) PHOBIAS	Anxiety
Eu40213	[X]CLAUSTROPHOBIA	Anxiety
Eu40214	[X]SIMPLE PHOBIA	Anxiety
Eu40y00	[X]OTHER PHOBIC ANXIETY DISORDERS	Anxiety
Eu40z00	[X]PHOBIC ANXIETY DISORDER; UNSPECIFIED	Anxiety
Eu40z11	[X]PHOBIA NOS	Anxiety
Eu40z12	[X]PHOBIC STATE NOS	Anxiety
Eu41.00	[X]OTHER ANXIETY DISORDERS	Anxiety
Eu41100	[X]GENERALIZED ANXIETY DISORDER	Anxiety
Eu41111	[X]ANXIETY NEUROSIS	Anxiety
Eu41112	[X]ANXIETY REACTION	Anxiety
Eu41113	[X]ANXIETY STATE	Anxiety
Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER	Anxiety
Eu41211	[X]MILD ANXIETY DEPRESSION	Anxiety
Eu41300	[X]OTHER MIXED ANXIETY DISORDERS	Anxiety
Eu41y00	[X]OTHER SPECIFIED ANXIETY DISORDERS	Anxiety
Eu41y11	[X]ANXIETY HYSTERIA	Anxiety
Eu41z00	[X]ANXIETY DISORDER; UNSPECIFIED	Anxiety
Eu41z11	[X]ANXIETY NOS	Anxiety
Eu42.00	[X]OBSESSIVE - COMPULSIVE DISORDER	Anxiety
Eu42.12	[X]OBSESSIVE-COMPULSIVE NEUROSIS	Anxiety
Eu42000	[X]PREDOMINANTLY OBSESSONAL THOUGHTS OR RUMINATIONS	Anxiety
Eu42100	[X]PREDOMINANTLY COMPULSIVE ACTS [OBSESSONAL RITUALS]	Anxiety
Eu42200	[X]MIXED OBSESSONAL THOUGHTS AND ACTS	Anxiety
Eu42y00	[X]OTHER OBSESSIVE-COMPULSIVE DISORDERS	Anxiety
Eu42z00	[X]OBSESSIVE-COMPULSIVE DISORDER; UNSPECIFIED	Anxiety
Eu43.00	[X]REACTION TO SEVERE STRESS; AND ADJUSTMENT DISORDERS	Anxiety
Eu43000	[X]ACUTE STRESS REACTION	Anxiety
Eu43011	[X]ACUTE CRISIS REACTION	Anxiety
Eu43012	[X]ACUTE REACTION TO STRESS	Anxiety
Eu43013	[X]COMBAT FATIGUE	Anxiety
Eu43014	[X]CRISIS STATE	Anxiety
Eu43015	[X]PSYCHIC SHOCK	Anxiety
Eu43100	[X]POST - TRAUMATIC STRESS DISORDER	Anxiety
Eu43111	[X]TRAUMATIC NEUROSIS	Anxiety
Eu43200	[X]ADJUSTMENT DISORDERS	Anxiety
Eu43300	[X]ACUTE POST-TRAUMATIC STRESS DISORDER FOLLOW MILITARY COMB	Anxiety
Eu43400	[X]CHRON POST-TRAUMATIC STRESS DISORDER FOLLOW MILITARY COMB	Anxiety
Eu43y00	[X]OTHER REACTIONS TO SEVERE STRESS	Anxiety
Eu43z00	[X]REACTION TO SEVERE STRESS; UNSPECIFIED	Anxiety
Eu44.00	[X]DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44.11	[X]CONVERSION HYSTERIA	Anxiety
Eu44.12	[X]CONVERSION REACTION	Anxiety
Eu44.13	[X]HYSTERIA	Anxiety
Eu44000	[X]DISSOCIATIVE AMNESIA	Anxiety
Eu44100	[X]DISSOCIATIVE FUGUE	Anxiety
Eu44200	[X]DISSOCIATIVE STUPOR	Anxiety
Eu44300	[X]TRANCE AND POSSESSION DISORDERS	Anxiety
Eu44400	[X]DISSOCIATIVE MOTOR DISORDERS	Anxiety
Eu44411	[X]PSYCHOGENIC APHONIA	Anxiety
Eu44412	[X]PSYCHOGENIC DYSPHONIA	Anxiety
Eu44500	[X]DISSOCIATIVE CONVULSIONS	Anxiety
Eu44511	[X]PSEUDOSEIZURES	Anxiety
Eu44600	[X]DISSOCIATIVE ANAESTHESIA AND SENSORY LOSS	Anxiety

Eu44611	[X]PSYCHOGENIC DEAFNESS	Anxiety
Eu44700	[X]MIXED DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44y00	[X]OTHER DISSOCIATIVE [CONVERSION] DISORDERS	Anxiety
Eu44y11	[X]GANSER'S SYNDROME	Anxiety
Eu44y12	[X]MULTIPLE PERSONALITY	Anxiety
Eu44y13	[X]PSYCHOGENIC CONFUSION	Anxiety
Eu44y14	[X]PSYCHOGENIC TWILIGHT STATE	Anxiety
Eu44z00	[X]DISSOCIATIVE [CONVERSION] DISORDER; UNSPECIFIED	Anxiety
Eu45.00	[X]SOMATOFORM DISORDERS	Anxiety
Eu45000	[X]SOMATIZATION DISORDER	Anxiety
Eu45011	[X]MULTIPLE PSYCHOSOMATIC DISORDER	Anxiety
Eu45012	[X]BRIQUET'S SYNDROME	Anxiety
Eu45100	[X]UNDIFFERENTIATED SOMATOFORM DISORDER	Anxiety
Eu45111	[X]UNDIFFERENTIATED PSYCHOSOMATIC DISORDER	Anxiety
Eu45200	[X]HYPOCHONDRIACAL DISORDER	Anxiety
Eu45211	[X]BODY DYSMORPHIC DISORDER	Anxiety
Eu45212	[X]DYSMORPHOPHOBIA NONDELUSIONAL	Anxiety
Eu45213	[X]HYPOCHONDRIACAL NEUROSIS	Anxiety
Eu45214	[X]HYPOCHONDRIASIS	Anxiety
Eu45300	[X]SOMATOFORM AUTONOMIC DYSFUNCTION	Anxiety
Eu45311	[X]CARDIAC NEUROSIS	Anxiety
Eu45312	[X]DA COSTA'S SYNDROME	Anxiety
Eu45313	[X]GASTRIC NEUROSIS	Anxiety
Eu45316	[X]PSYCHOGENIC COUGH	Anxiety
Eu45317	[X]PSYCHOGENIC DIARRHOEA	Anxiety
Eu45318	[X]PSYCHOGENIC DYSPEPSIA	Anxiety
Eu45319	[X]PSYCHOGENIC DYSURIA	Anxiety
Eu45320	[X]PSYCHOGENIC FLATULENCE	Anxiety
Eu45321	[X]PSYCHOGENIC HICCUGH	Anxiety
Eu45322	[X]PSYCHOGENIC HYPERVENTILAT	Anxiety
Eu45323	[X]PSYCHOGENIC FREQ MICTURIT	Anxiety
Eu45324	[X]PSYCHOGENIC IBS	Anxiety
Eu45400	[X]PERSISTENT SOMATOFORM PAIN DISORDER	Anxiety
Eu45411	[X]PSYCHALGIA	Anxiety
Eu45412	[X]PSYCHOGENIC BACKACHE	Anxiety
Eu45413	[X]PSYCHOGENIC HEADACHE	Anxiety
Eu45414	[X]SOMATOFORM PAIN DISORDER	Anxiety
Eu45500	[X]GLOBUS PHARYNGEUS	Anxiety
Eu45511	[X]GLOBUS HYSTERICUS	Anxiety
Eu45y00	[X]OTHER SOMATOFORM DISORDERS	Anxiety
Eu45y11	[X]PSYCHOGENIC DYSMENORRHOEA	Anxiety
Eu45y12	[X]GLOBUS HYSTERICUS	Anxiety
Eu45y13	[X]PSYCHOGENIC PRURITIS	Anxiety
Eu45y14	[X]PSYCHOGENIC TORTICOLLIS	Anxiety
Eu45z00	[X]SOMATOFORM DISORDER; UNSPECIFIED	Anxiety
Eu45z11	[X]PSYCHOSOMATIC DISORDER NOS	Anxiety
Eu46.00	[X]OTHER NEUROTIC DISORDERS	Anxiety
Eu46000	[X]NEURASTHENIA	Anxiety
Eu46011	[X]FATIGUE SYNDROME	Anxiety
Eu46100	[X]DEPERSONALIZATION - DEREALIZATION SYNDROME	Anxiety
Eu46y00	[X]OTHER SPECIFIED NEUROTIC DISORDERS	Anxiety
Eu46y12	[X]DHAT SYNDROME	Anxiety
Eu46y13	[X]OCCUPATIONAL NEUROSIS; INCLUDING WRITER'S CRAMP	Anxiety
Eu46y16	[X]PSYCHOGENIC SYNCOPE	Anxiety
Eu46z00	[X]NEUROTIC DISORDER; UNSPECIFIED	Anxiety
Eu46z11	[X]NEUROSIS NOS	Anxiety
Eu51511	[X]DREAM ANXIETY DISORDER	Anxiety
Eu60600	[X]Anxious [avoidant] personality disorder	Anxiety
Eu93000	[X]SEPARATION ANXIETY DISORDER OF CHILDHOOD	Anxiety
Eu93100	[X]Phobic anxiety disorder of childhood	Anxiety
Eu93200	[X]SOCIAL ANXIETY DISORDER OF CHILDHOOD	Anxiety
Z4L1.00	ANXIETY COUNSELLING	Anxiety
1B1V.00	C/O - panic attack	Panic
225J.00	O/E - PANIC ATTACK	Panic
E200100	PANIC DISORDER	Panic
E200111	PANIC ATTACK	Panic
E202100	AGORAPHOBIA WITH PANIC ATTACKS	Panic

EMA PROTOCOL

E202200	AGORAPHOBIA WITHOUT MENTION OF PANIC ATTACKS	Panic
E280.00	ACUTE PANIC STATE DUE TO ACUTE STRESS REACTION	Panic
Eu40012	[X]PANIC DISORDER WITH AGORAPHOBIA	Panic
Eu41000	[X]PANIC DISORDER [EPISODIC PAROXYSMAL ANXIETY]	Panic
Eu41011	[X]PANIC ATTACK	Panic
Eu41012	[X]PANIC STATE	Panic
1B1O.00	RESTLESS	Restlessness
E274D11	RESTLESS SLEEP	Restlessness
F13z200	RESTLESS LEGS SYNDROME	Restlessness
R00zD00	[D]RESTLESSNESS AND AGITATION	Restlessness
1B1B.00	CANNOT SLEEP - INSOMNIA	Sleep
1B1B.11	C/O - INSOMNIA	Sleep
1B1B000	INITIAL INSOMNIA	Sleep
1B1B100	MIDDLE INSOMNIA	Sleep
1B1B200	LATE INSOMNIA	Sleep
1B1Q.00	POOR SLEEP PATTERN	Sleep
1BX0.00	DELAYED ONSET OF SLEEP	Sleep
1BX1.00	EXCESSIVE SLEEP	Sleep
1BX9.00	LIGHT SLEEP	Sleep
8G99.00	SLEEP RESTRICTION THERAPY	Sleep
8HTn.00	REFERRAL TO SLEEP CLINIC	Sleep
8Q0..00	SLEEP MANAGEMENT	Sleep
9b9Y.00	SLEEP STUDIES - SPECIALTY	Sleep
9Ngt.00	ON MELATONIN FOR SLEEP DISORDER	Sleep
9Nk0.00	SEEN IN SLEEP CLINIC	Sleep
E274.00	NON-ORGANIC SLEEP DISORDERS	Sleep
E274.12	INSOMNIA DUE TO NONORGANIC SLEEP DISORDER	Sleep
E274000	UNSPECIFIED NON-ORGANIC SLEEP DISORDER	Sleep
E274100	TRANSIENT INSOMNIA	Sleep
E274111	INSOMNIA NOS	Sleep
E274200	PERSISTENT INSOMNIA	Sleep
E274700	SOMNAMBULISM - SLEEP WALKING	Sleep
E274A00	SLEEP DRUNKENNESS	Sleep
E274B00	REPEATED RAPID EYE MOVEMENT SLEEP INTERRUPTIONS	Sleep
E274C00	OTHER SLEEP STAGE OR AROUSAL DYSFUNCTION	Sleep
E274D00	REPETITIVE INTRUSIONS OF SLEEP	Sleep
E274E00	"SHORT-SLEEPER"	Sleep
E274F00	INVERSION OF SLEEP RHYTHM	Sleep
E274y00	OTHER NON-ORGANIC SLEEP DISORDER	Sleep
E274z00	NON-ORGANIC SLEEP DISORDER NOS	Sleep
Eu51.00	[X]NONORGANIC SLEEP DISORDERS	Sleep
Eu51000	[X]NONORGANIC INSOMNIA	Sleep
Eu51200	[X]NONORGANIC DISORDER OF THE SLEEP-WAKE SCHEDULE	Sleep
Eu51300	[X]SLEEPWALKING	Sleep
Eu51400	[X]SLEEP TERRORS	Sleep
Eu51y00	[X]OTHER NONORGANIC SLEEP DISORDERS	Sleep
Eu51z00	[X]NONORGANIC SLEEP DISORDER, UNSPECIFIED	Sleep
Eu51z11	[X]EMOTIONAL SLEEP DISORDER NOS	Sleep
Fy0..00	SLEEP DISORDERS	Sleep
Fy00.00	DISORDERS OF INITIATING AND MAINTAINING SLEEP	Sleep
Fy02.00	DISORDERS OF THE SLEEP-WAKE SCHEDULE	Sleep
Fy03.00	SLEEP APNOEA	Sleep
Fy03.11	OBSTRUCTIVE SLEEP APNOEA	Sleep
Fy04.00	SLEEP-RELATED RESPIRATORY FAILURE	Sleep
Fy05.00	NOCTURNAL SLEEP-RELATED EATING DISORDER	Sleep
Fyu5800	[X]OTHER SLEEP DISORDERS	Sleep
H5B..00	SLEEP APNOEA	Sleep
K5A2100	MENOPAUSAL SLEEPLESSNESS	Sleep
R005.00	[D]SLEEP DISTURBANCES	Sleep
R005.11	[D]INSOMNIA - SYMPTOM	Sleep
R005.12	[D]SLEEP RHYTHM PROBLEMS	Sleep
R005000	[D]SLEEP DISTURBANCE, UNSPECIFIED	Sleep
R005100	[D]INSOMNIA WITH SLEEP APNOEA	Sleep
R005100	[D]INSOMNIA WITH SLEEP APNOEA	Sleep
R005200	[D]INSOMNIA NOS	Sleep
R005300	[D]HYPERMOMNIA WITH SLEEP APNOEA	Sleep
R005311	[D]SLEEP APNOEA SYNDROME	Sleep

R005312	[D]SYNDROME SLEEP APNOEA	Sleep
R005500	[D]SLEEP RHYTHM INVERSION	Sleep
R005600	[D]SLEEP RHYTHM IRREGULAR	Sleep
R005900	[D]SLEEP DYSFUNCTION WITH AROUSAL DISTURBANCE	Sleep
R005200	[D]SLEEP DYSFUNCTION NOS	Sleep
T163.00	MOTOR VEHICLE TRAFFIC ACCIDENT DUE TO MOTOR VEHICLE GOING OUT OF CONTROL DUE TO DRIVER FALLING ASLEEP, WITHOUT COLLISION ON THE HIGHWAY	Sleep
Z1M..00	SLEEP AND REST INTERVENTIONS	Sleep
ZV1B100	[V]PERSONAL HISTORY OF UNHEALTHY SLEEP-WAKE SCHEDULE	Sleep
1B17.00	DEPRESSED	Depression
62T1.00	PUERPERAL DEPRESSION	Depression
9KQ..00	ON FULL DOSE LONG TERM TREATMENT DEPRESSION - ENH SERV ADMIN	Depression
E001300	PRESENILE DEMENTIA WITH DEPRESSION	Depression
E002100	SENILE DEMENTIA WITH DEPRESSION	Depression
E004300	ARTERIOSCLEROTIC DEMENTIA WITH DEPRESSION	Depression
E11..12	DEPRESSIVE PSYCHOSES	Depression
E112.00	SINGLE MAJOR DEPRESSIVE EPISODE	Depression
E112.11	AGITATED DEPRESSION	Depression
E112.12	ENDOGENOUS DEPRESSION FIRST EPISODE	Depression
E112.13	ENDOGENOUS DEPRESSION FIRST EPISODE	Depression
E112.14	ENDOGENOUS DEPRESSION	Depression
E112000	SINGLE MAJOR DEPRESSIVE EPISODE; UNSPECIFIED	Depression
E112100	SINGLE MAJOR DEPRESSIVE EPISODE; MILD	Depression
E112200	SINGLE MAJOR DEPRESSIVE EPISODE; MODERATE	Depression
E112300	SINGLE MAJOR DEPRESSIVE EPISODE; SEVERE; WITHOUT PSYCHOSIS	Depression
E112400	SINGLE MAJOR DEPRESSIVE EPISODE; SEVERE; WITH PSYCHOSIS	Depression
E112z00	SINGLE MAJOR DEPRESSIVE EPISODE NOS	Depression
E113.00	RECURRENT MAJOR DEPRESSIVE EPISODE	Depression
E113.11	ENDOGENOUS DEPRESSION - RECURRENT	Depression
E113000	RECURRENT MAJOR DEPRESSIVE EPISODES; UNSPECIFIED	Depression
E113100	RECURRENT MAJOR DEPRESSIVE EPISODES; MILD	Depression
E113200	RECURRENT MAJOR DEPRESSIVE EPISODES; MODERATE	Depression
E113300	RECURRENT MAJOR DEPRESSIVE EPISODES; SEVERE; NO PSYCHOSIS	Depression
E113400	RECURRENT MAJOR DEPRESSIVE EPISODES; SEVERE; WITH PSYCHOSIS	Depression
E113700	RECURRENT DEPRESSION	Depression
E113z00	RECURRENT MAJOR DEPRESSIVE EPISODE NOS	Depression
E118.00	SEASONAL AFFECTIVE DISORDER	Depression
E11y200	ATYPICAL DEPRESSIVE DISORDER	Depression
E11z200	MASKED DEPRESSION	Depression
E135.00	AGITATED DEPRESSION	Depression
E200300	ANXIETY WITH DEPRESSION	Depression
E204.00	NEUROTIC DEPRESSION REACTIVE TYPE	Depression
E204.11	POSTNATAL DEPRESSION	Depression
E290.00	BRIEF DEPRESSIVE REACTION	Depression
E290z00	BRIEF DEPRESSIVE REACTION NOS	Depression
E291.00	PROLONGED DEPRESSIVE REACTION	Depression
E2B..00	DEPRESSIVE DISORDER NEC	Depression
E2B0.00	POSTVIRAL DEPRESSION	Depression
E2B1.00	CHRONIC DEPRESSION	Depression
Eu20400	[X]POST-SCHIZOPHRENIC DEPRESSION	Depression
Eu32.00	[X]DEPRESSIVE EPISODE	Depression
Eu32.11	[X]SINGLE EPISODE OF DEPRESSIVE REACTION	Depression
Eu32.12	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSION	Depression
Eu32.13	[X]SINGLE EPISODE OF REACTIVE DEPRESSION	Depression
Eu32000	[X]MILD DEPRESSIVE EPISODE	Depression
Eu32100	[X]MODERATE DEPRESSIVE EPISODE	Depression
Eu32200	[X]SEVERE DEPRESSIVE EPISODE WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu32211	[X]SINGLE EPISODE AGITATED DEPRESSN W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32212	[X]SINGLE EPISODE MAJOR DEPRESSION W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32213	[X]SINGLE EPISODE VITAL DEPRESSION W'OUT PSYCHOTIC SYMPTOMS	Depression
Eu32300	[X]SEVERE DEPRESSIVE EPISODE WITH PSYCHOTIC SYMPTOMS	Depression
Eu32311	[X]SINGLE EPISODE OF MAJOR DEPRESSION AND PSYCHOTIC SYMPTOMS	Depression
Eu32312	[X]SINGLE EPISODE OF PSYCHOGENIC DEPRESSIVE PSYCHOSIS	Depression
Eu32313	[X]SINGLE EPISODE OF PSYCHOTIC DEPRESSION	Depression
Eu32314	[X]SINGLE EPISODE OF REACTIVE DEPRESSIVE PSYCHOSIS	Depression
Eu32400	[X]MILD DEPRESSION	Depression
Eu32500	[X]MAJOR DEPRESSION; MILD	Depression

Eu32600	[X]MAJOR DEPRESSION; MODERATELY SEVERE	Depression
Eu32700	[X]MAJOR DEPRESSION; SEVERE WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu32800	[X]MAJOR DEPRESSION; SEVERE WITH PSYCHOTIC SYMPTOMS	Depression
Eu32900	[X]SINGLE MAJOR DEPR EP; SEVERE WITH PSYCH; PSYCH IN REMISS	Depression
Eu32A00	[X]RECURR MAJOR DEPR EP; SEVERE WITH PSYCH; PSYCH IN REMISS	Depression
Eu32y00	[X]OTHER DEPRESSIVE EPISODES	Depression
Eu32y11	[X]ATYPICAL DEPRESSION	Depression
Eu32y12	[X]SINGLE EPISODE OF MASKED DEPRESSION NOS	Depression
Eu32z00	[X]DEPRESSIVE EPISODE; UNSPECIFIED	Depression
Eu32z11	[X]DEPRESSION NOS	Depression
Eu32z12	[X]DEPRESSIVE DISORDER NOS	Depression
Eu32z13	[X]PROLONGED SINGLE EPISODE OF REACTIVE DEPRESSION	Depression
Eu32z14	[X] REACTIVE DEPRESSION NOS	Depression
Eu33.00	[X]RECURRENT DEPRESSIVE DISORDER	Depression
Eu33.11	[X]RECURRENT EPISODES OF DEPRESSIVE REACTION	Depression
Eu33.12	[X]RECURRENT EPISODES OF PSYCHOGENIC DEPRESSION	Depression
Eu33.13	[X]RECURRENT EPISODES OF REACTIVE DEPRESSION	Depression
Eu33.14	[X]SEASONAL DEPRESSIVE DISORDER	Depression
Eu33.15	[X]SAD - SEASONAL AFFECTIVE DISORDER	Depression
Eu33000	[X]RECURRENT DEPRESSIVE DISORDER; CURRENT EPISODE MILD	Depression
Eu33100	[X]RECURRENT DEPRESSIVE DISORDER; CURRENT EPISODE MODERATE	Depression
Eu33200	[X]RECURR DEPRESS DISORDER CUR EPI SEVERE WITHOUT PSYC SYMPT	Depression
Eu33211	[X]ENDOGENOUS DEPRESSION WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33212	[X]MAJOR DEPRESSION; RECURRENT WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33214	[X]VITAL DEPRESSION; RECURRENT WITHOUT PSYCHOTIC SYMPTOMS	Depression
Eu33300	[X]RECURRENT DEPRESS DISORDER CUR EPI SEVERE WITH PSYC SYMP	Depression
Eu33311	[X]ENDOGENOUS DEPRESSION WITH PSYCHOTIC SYMPTOMS	Depression
Eu33312	[X]MANIC-DEPRESS PSYCHOSIS;DEPRESSED TYPE+PSYCHOTIC SYMPTOMS	Depression
Eu33313	[X]RECURR SEVERE EPISODES/MAJOR DEPRESSION+PSYCHOTIC SYMPTOM	Depression
Eu33314	[X]RECURR SEVERE EPISODES/PSYCHOGENIC DEPRESSIVE PSYCHOSIS	Depression
Eu33315	[X]RECURRENT SEVERE EPISODES OF PSYCHOTIC DEPRESSION	Depression
Eu33316	[X]RECURRENT SEVERE EPISODES/REACTIVE DEPRESSIVE PSYCHOSIS	Depression
Eu33400	[X]RECURRENT DEPRESSIVE DISORDER; CURRENTLY IN REMISSION	Depression
Eu33y00	[X]OTHER RECURRENT DEPRESSIVE DISORDERS	Depression
Eu33z00	[X]RECURRENT DEPRESSIVE DISORDER; UNSPECIFIED	Depression
Eu33z11	[X]MONOPOLAR DEPRESSION NOS	Depression
Eu34100	[X]DYSTHYMIA	Depression
Eu34111	[X]DEPRESSIVE NEUROSIS	Depression
Eu34113	[X]NEUROTIC DEPRESSION	Depression
Eu3y111	[X]RECURRENT BRIEF DEPRESSIVE EPISODES	Depression
Eu41200	[X]MIXED ANXIETY AND DEPRESSIVE DISORDER	Depression
Eu41211	[X]MILD ANXIETY DEPRESSION	Depression
Eu53011	[X]POSTNATAL DEPRESSION NOS	Depression
Eu53012	[X]POSTPARTUM DEPRESSION NOS	Depression
Eu92000	[X]DEPRESSIVE CONDUCT DISORDER	Depression

Annex E Format of analysis datasets

The analysis datasets will be constructed from several data extractions.

D1 The prescription of any LNG IUD and demographic details at the time of prescription will be written to IUDSTUDY_LNGIUDvvvv (where vvvv is the version of THIN).

D2 The prescription of any non-LNG IUD and demographic details at the time of prescription will be written to IUDSTUDY_OTH IUDvvvv (where vvvv is the version of THIN).

D3 From the combined list of IUD prescriptions women will be selected with a full year of observation prior to the first recorded IUD prescription. From these, women with either an IUD removal or replacement code up to and including the prescription date will be excluded. The resulting list of 'first' prescriptions will be named FIRSTIUD.

For any woman listed in FIRSTIUD the following data will be extracted

D4 Any Read code related to anxiety, sleep problems, restlessness or panic. [Note that depression symptoms will also be extracted for a subsidiary analysis]

D5 Any read code related to anaemia, endometriosis, menorrhagia, other menstrual bleeding problems, premenstrual syndrome, dysmenorrhoea, or menopausal problems (without menorrhagia).

ANALYSIS DATASET

From the above datasets the following variables will be extracted

PRACID	Practice ID
PATID	Patient ID
DOB	Date of birth
REGDATE	Registration date
FINALDATE	Patient end of follow-up
DEATHDATE	Date of death
GROUP	Study treatment group
DATEFIRSTTRT	Date of insertion of study IUD
DATELASTTRT	Date of end of study exposure
AGE0	Age at insertion of study IUD
<Outcome variables >	
OUTCANY	1 if any of anxiety, restlessness, sleep disorder, panic after insertion.
TANY	Time (days) of first record of any symptom or EOF
ANX	1 if any anxiety after insertion
TANX	Time (days) of first anxiety symptom or EOF
REST	1 if any restlessness symptom after insertion
TREST	Time (days) of first restlessness symptom or EOF
PAN	1 if any panic symptom after insertion

TPAN	Time (days) of first panic symptom or EOF
SLEEP	1 if any sleep problem after insertion
TSLEEP	Time (days) of first sleep symptom or EOF
<Pre-exposure occurrence of study outcome symptoms >	
ANX0	Any anxiety symptom in year before exposure
REST0	Any restlessness symptom in year before exposure
PAN0	Any panic symptom in year before exposure
SLEEP0	Any sleep problem symptom in year before exposure
< Potential confounders >	
ANAEMIA1	Anaemia in year before insertion
ANAEMIAEV	Anaemia ever before insertion
ENDOMET1	Endometriosis in year before insertion
ENDOMETEV	Endometriosis ever before insertion
MENOR1	Menorrhagia in year before insertion
MENOREV	Menorrhagia ever before insertion
DYSMEN1	Dysmenorrhagia in year before insertion
DYSMENEV	Dysmenorrhagia ever before insertion
OTHMEN1	Other menstruation problem in year before insertion
OTHMENEV	Other menstruation problem ever before insertion
PMS1	PMS in year before insertion
PMSEV	PMS ever before insertion
MPAUS1	Menopausal problem (not dysmenorrhagic) in year before insertion
MPAUSEV	Menopausal problem (not dysmenorrhagic) ever before insertion
<Exposure to other relevant treatments in year prior to study>	
ANXIOLYTICS1	
ANTIDEP1	
ANTIPSYCH1	
INHALER1	
ORALCONT1	
TRANEXAMIC1	
BENZODIAZ1	
<Other baseline>	
DEPRIVATION	
SMOKING	Current recorded smoking status

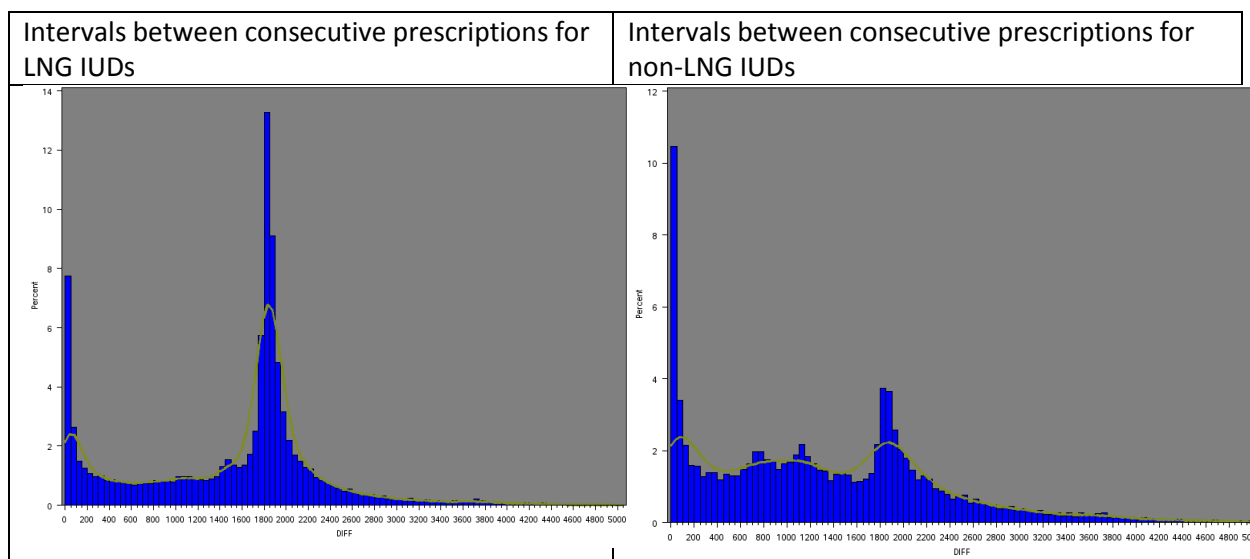
Sensitivity analysis datasets

Two datasets will be created, one for the main analysis (IUDMAIN) and one for the sensitivity analysis in which all women with difficult to interpret Read codes are excluded (IUDSENS) – see discussion under data cleaning (Annex G).

Annex F. Description of populations for selection of treatment and comparator group – based on THIN 1605

Annual numbers of women prescribed contraceptives

Obs	YEAR	PRESC	LNG IUDs	Other IUDs
1	1995		295	3476
2	1996		928	3674
3	1997		1277	3771
4	1998		2057	3868
5	1999		2622	3835
6	2000		3546	3688
7	2001		4596	3419
8	2002		5370	3731
9	2003		6253	3661
10	2004		7026	3686
11	2005		8230	3717
12	2006		9261	3824
13	2007		10123	3777
14	2008		10981	3946
15	2009		12408	3775
16	2010		13588	4026
17	2011		14102	4138
18	2012		13798	3932
19	2013		12847	3580
20	2014		11679	3145
21	2015		9313	2517
22	2016		2642	682



Annex G Notes on cleaning data

Prescription codes

This study relies on accurate use of the codes for LNG and non-LNG IUDs. It is probable that the codes for LNG IUDs are accurately used but the codes that simply denote an IUD could occasionally be used for LNG-IUDs. In the THIN1605 dataset 406 women have codes for both LNG and non-LNG IUDs on the same date, suggesting that some confusion may have occurred. Rather than making arbitrary assumptions, such prescriptions will be omitted from the study.

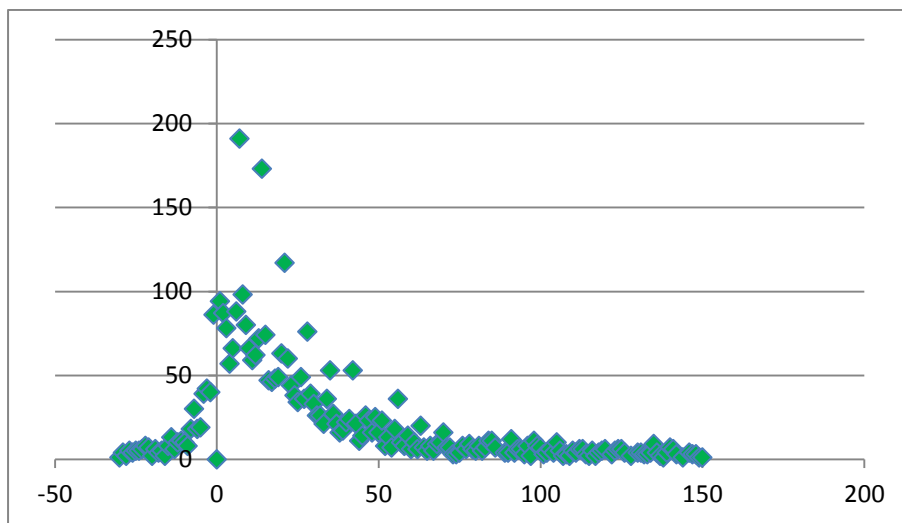
A smaller number of women have codes for both the 52mg and the 13.5mg LNG IUD on the same day. These cases have been coded as 52mg – which is very much more common than 13.5 – but a column has been added to the dataset (DoseAlt) coding them to 13.5 for sensitivity analyses of any dose related calculations.

IUD associated Read codes

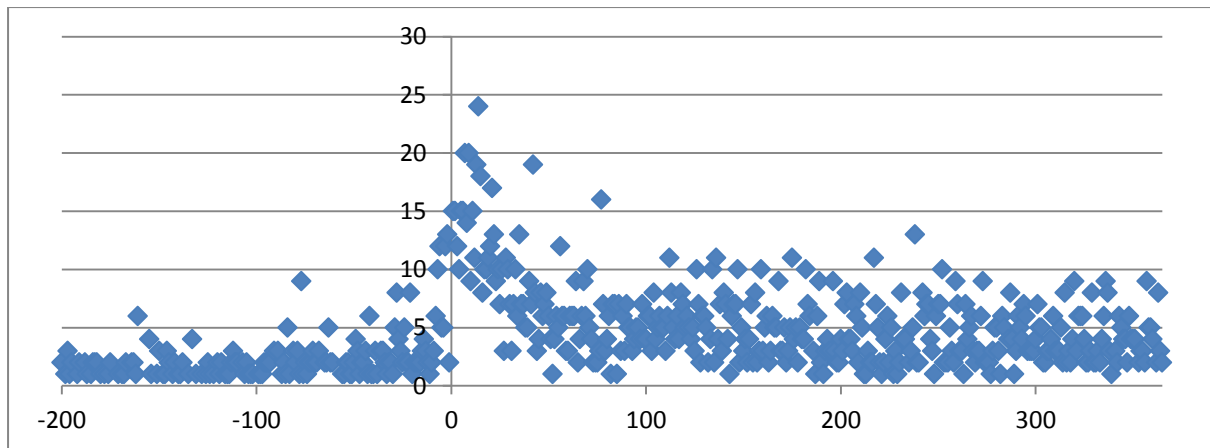
A number of Read codes related to IUDs may also help to determine if a first prescription is truly first use – not that this is essential for the study but it would be required to avoid direct continuity with a previous IUD exposure – and also to determine the duration of use of IUD prescriptions included in the study. These Read codes can be grouped into those related to insertion, removal, replacement, checks on or advice concerning IUDs. Advice codes do not imply current use of a device but checks, removal and replacement do.

These Read codes require some cautious interpretation. The distribution of time intervals between the dates on which an insertion code is recorded and the first recorded prescription of an IUD is shown below. A count of about 7000 at 0 days has been excluded so the scale can be discerned. It is clear that the code is used increasingly from about 30 days before the prescription. Clearly, in these cases the date of recording the insertion is not the date of insertion but, more likely, the date on which the decision to use an IUD was made. This calls into question whether the dates following the prescription can be considered informative regarding when the IUD was inserted or if they are when the GP recorded that the device had been inserted. Given these doubts and the fact that the overwhelming number of prescriptions either do not have an insertion coded or have it coded on the same day, the study start date is set to the prescription date in all cases.

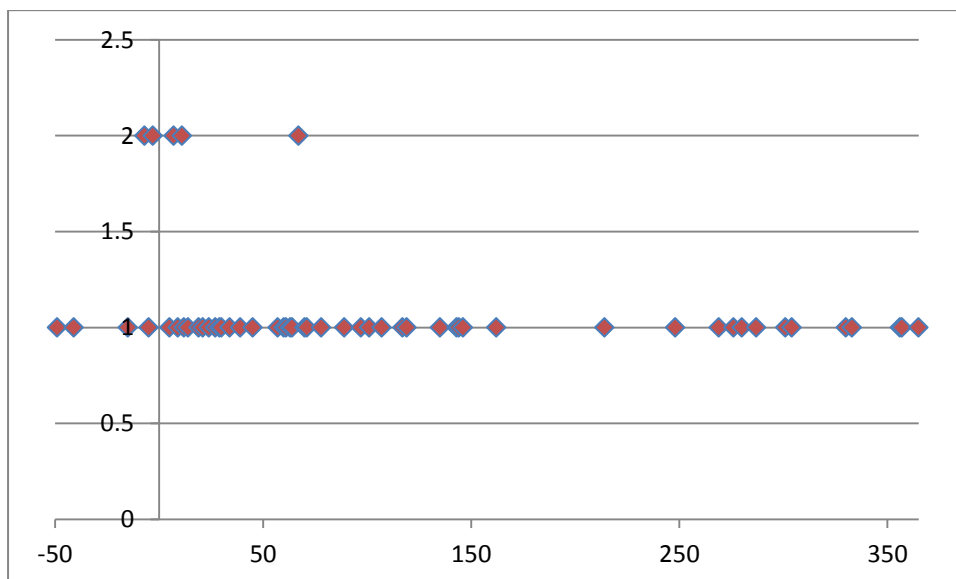
INSERTION v DAYS FROM PRESCRIPTION- PEAK AT T=0 OF 7239 (Not shown)



REMOVAL v DAYS FROM PRESCRIPTION - PEAK AT T=0 OF 499 (Not shown)



REPLACEMENT v DAYS FROM PRESCRIPTION - PEAK AT T=0 OF 129 (Not shown)



A further confusing observation is that a number of cases exist where a code for insertion is used that is not adjacent to any prescription code. There are 34005 Read codes for insertion and only 12866 are within 30 days of a prescription for an IUD. This should be viewed in the context of 212022 such prescriptions. There is no way of using these Read codes to add to the study population as they do not reveal the type of IUD. However, they may inform concerning the use of IUDs. However, it is also possible that they reflect discussion about potential use of an IUD that was eventually not adopted.

Read codes for removal also start to increase shortly before the prescription date and show a brief peak before settling to a fairly constant level. The pre-prescription codes probably indicate removal of a previous device – there is a count of about 500 on day 0 which is not shown in the graph. However, removal after the prescription is less clear. It could be removal of a previous device preparatory to fitting the new IUD or it could reflect a problem with the new device. The difficulty of accurately interpreting both insertion and removal codes suggests that the uncertainty might be best handled by a sensitivity analysis as follows:

1. All patients with a removal or replacement code before or on day 0 would be excluded from the study.
2. Patients with removal or insertion codes soon after the prescription date would be included in the main analysis. Such patients would be excluded in a sensitivity analysis. Removal codes 6 months or more following the prescription will be taken literally to reflect the end of exposure and the woman retained in the main analysis.

If such a code, or one concerning removal or checking of an IUD, has been recorded in the year before the first recorded prescription of an IUD it is assumed that the woman is already using an IUD and is excluded from the study. There are a number of women for whom the insertion date is recorded a few days before the prescription. It is possible that this is some form of miscoding but these women are also removed. Likewise, if a removal or replacement is recorded on the same day as the prescription these cases are excluded.

The end of a period of use of an IUD can be indicated by a removal code or a further insertion or replacement code or prescription of another contraceptive. It is also possible that the removal will not be indicated in any way. The doubts about the use of these codes soon after the prescription makes them very difficult to use. These cases will thus be handled via the above sensitivity analysis.