Building a European prospective cycle-by-cycle registry for medically assisted reproduction – plan for the EuMAR pilot study

May 2024, EuMAR WP6

Introduction

The European monitoring of Medically Assisted Reproduction (EuMAR) project was initiated in 2023 with the aim to build the foundation for a pan-European prospective cycle-by-cycle registry of Medically Assisted Reproduction (MAR) treatments. The three objectives of the EuMAR project are 1) to construct a data flow model that is applicable in different contexts, 2) to create a set of core parameters to enhance data standardisation, and 3) to build a technical solution for the registry and for a unique European patient code that is compliant with the General Data Protection Regulation (GDPR). Detailed information on the rationale and objectives of the project has previously been published elsewhere (De Geyter et al., 2023).

The pilot study will be an important part of the EuMAR project, contributing to all three objectives by testing the feasibility of implementing the solutions developed for the different objectives in practice. This protocol provides a detailed description of the aims, outcomes, and materials and methods envisioned for the EuMAR pilot study.

Aims

The aim of the EuMAR pilot study is to test the practical implementation of the EuMAR data collection system, with a view to determining the feasibility of collecting prospective and cumulative cycle-by-cycle data on MAR treatments from different countries in a common European registry, including the possibility to link treatments of patients in different centres or countries.

Outcomes

The primary outcome of the EuMAR pilot study is the quality of the collected data, which is conceptualised across the following three dimensions: completeness and timeliness, internal consistency, and external consistency, i.e., whether the content of the data is in line with other data sources. This conceptualisation follows the model of a WHO framework for data quality assurance (WHO, 2022). The framework also includes the additional dimension "consistency of population data to be used as denominators in calculations"; however, this dimension was not considered relevant for the EuMAR pilot study, since it does not relate to the data collected in the registry itself. An overview of the indicators that will be assessed for each dimension of data quality is provided in table 1.

Dimension	**Indicator**	**Level of calculation**
Completeness and timeliness	% of centres offering MAR services in the pilot countries that reported any data to EuMAR	Overall, by country, by type of treatment offered (only IUI vs. also IVF/ICSI)
	% of eligible cycles registered in a clinic's medical records or in a national registry that were recorded in EuMAR (where possible)	By country or by clinic
	% of cycles in the EuMAR registry with complete follow-up (until one of the following defined endpoints: cancellation of the cycle, OPU with no oocytes retrieved, IVF/ICSI with no surviving embryos, cryopreservation of all oocytes/embryos, IUI/embryo transfer with no clinical pregnancy, pregnancy loss, delivery)	Overall, by country, residence status (cross-border vs. domestic), clinic, type of cycle,

	% of cycles in the EuMAR registry with complete data (complete follow-up and 0 missing values)	Overall, by country, residence status (cross-border vs. domestic), clinic, type of cycle
	% of missing values per parameter	Overall and by country and clinic
	% of patients for whom the IRCC was requested on time	Overall and by country and clinic
	% of cycles in the EuMAR registry for which data was received on time (within two months or within schedule of national registry)	Overall and by country and clinic
Internal consistency	Number of deviations from pre-set validation rules	Overall and by country, clinic and validation rule
	Number of duplicate/empty records	Overall and by country and clinic
External consistency	Calculation of derived parameters (see Annex 1) and qualitative comparison to national statistics, literature or previous EIM data where available	Overall and by country

Table 1: Indicators of data quality

The secondary outcomes of the EuMAR pilot study relate to the process of the data collection and include practical issues encountered and areas for improvement in the implementation of the EuMAR registry.

Materials and methods

Study design

This protocol describes a pilot study with data collection from national MAR registries and medical records.

Study setting

The EuMAR pilot study will take place in five different countries. The pilot countries were selected by the project steering committee based on information gathered through a survey and individual interviews with the institutions responsible for national data collection on MAR in EU Member States. The selection aims to cover the diversity of national data collection systems to ensure a possibility to test all the different modalities of submitting data to the EuMAR registry and implementing the unique patient code.

Study population

Ultimately, it is aimed for the EuMAR registry to include prospective data on all MAR treatments that involve the *ex vivo* handling of gametes or gonadal tissues, including in vitro fertilisation (IVF), intracytoplasmic sperm injection (ICSI), intrauterine insemination (IUI), preimplantation genetic testing (PGT) treatments, and fertility preservation through gamete/embryo/gonadal tissue cryopreservation. Thus, in addition to infertile patients, the registry will also include individuals having an oocyte pick-up (OPU) for the purpose of donation or fertility preservation, as well as surrogates. However, no data will be collected from sperm banks, meaning that sperm donors will not be included at this stage of the project. Individuals will be registered with a unique Individual Reproductive Care Code (IRCC) the first time they initiate a new cycle during the pilot study, i.e., an IUI, OPU, IVF/ICSI or embryo transfer, independent of whether the gametes or embryos used have been retrieved or created before the pilot study. If patients seek MAR treatment as a couple, both partners will receive an IRCC, independent of their biological involvement (i.e., including partners of recipients of a sperm donation). Further details on the IRCC will be provided in the section on data collection.

Study period

The pilot study will commence on 1 July 2024 and include all cycles that are initiated until 31 December 2024. Until 30 September 2025, follow-up data will be collected for all registered cycles until one of the defined cycle endpoints (cancellation of the cycle, OPU with no oocytes retrieved, IVF/ICSI with no surviving embryos, cryopreservation of all oocytes/embryos, IUI/embryo transfer with no clinical pregnancy, pregnancy loss, delivery).

Data collection

In countries with a national cycle-by-cycle registry, data will be collected through an Application Programming Interface (API), connecting the EuMAR registry with the national registry and thereby allowing for automatic data submission. In countries with no national cycle-by-cycle registry, API connections will be built with the Electronic Medical Record (EMR) systems of centres or, if no EMR system is used, data will be collected via manual input from centre staff into an online platform. The parameters on which data will be collected can be found in Annex 1. The timeline for data submission by national registries will be set together with the national registries, whereas clinics sending their data directly to EuMAR will be asked to submit the data within a period of no more than two months after the treatment/outcome occurred.

To allow for cumulative data analysis, each individual will be registered with a unique Individual Reproductive Care Code (IRCC), which needs to be provided when submitting data to the national registry or directly to the EuMAR registry. The IRCC can be requested by the centre as soon as the treatment is planned. For cycles with ovarian stimulation, it needs to be requested at the latest five days after the start of medication. For cycles without ovarian stimulation, the IRCC needs to be requested at the latest on the day where the first step of the treatment is performed, i.e., for IUI cycles on the day of the IUI, for natural cycle IVF on the day of the OPU, for cycles with cryopreserved or donor oocytes on the day of the fertilisation of the oocyte, and for frozen embryo transfers on the day of thawing the embryos. While oocyte donors will receive an IRCC, there will be no link in the registry between donation cycles and the subsequent IVF/ICSI and embryo transfer in recipients, unless in the case of the reception of oocytes from a same sex partner (ROPA). Likewise, it will not be possible to connect data on the OPU and IVF/ICSI of intended parents in surrogacy with data on the embryo transfer and pregnancy in the surrogate. To increase data protection, the IRCC will go through a one-way encryption process to be transformed into a different unique code when it is sent to the EuMAR registry.

For cross-institutional and cross-border follow-up, individuals who change centres are asked to request a ClinicSwitch code from their old centre and present it at the new centre, which allows linking the data submitted by the new centre with the existing record of the person in

the EuMAR registry. If a couple changes centres, a separate ClinicSwitch code needs to be provided for each partner. Centres will not be able to see any data entered by other centres in the database. However, in centres who enter data manually, the option of sharing a standardised report of the data submitted to the EuMAR registry along with the ClinicSwitch code will be explored, which patients can present to their clinician at the next centre if they wish to do so. The technical flow of the IRCC and ClinicSwitch code in different scenarios is presented in Annex 2.

The EuMAR support staff at the ESHRE central office will document information on practical issues encountered during the study in a logbook.

Data analysis

In line with the recommendations for pilot and feasibility studies (Lancaster, Dodd, & Williamson, 2004), the data will only be analysed descriptively and no statistical inference will be carried out. The descriptive statistics that will be provided include the number of IRCCs requested, the number of cycles recorded, the number of ClinicSwitch codes requested, the number of ClinicSwitch codes scanned, all the indicators of data quality presented in table 1, as well as all the derived output parameters specified in Annex 1.

Data management and monitoring

The data will be managed by ESHRE and will only be accessible to authorised ESHRE experts and staff, as well as the IT company subcontracted to build the registry. A professional law firm was subcontracted to prepare a data protection impact assessment (DPIA) prior to the start of the study. This legal analysis concluded that the data in the EuMAR registry can be considered anonymous, since it will be impossible for ESHRE to identify individual patients due to the one-way encryption of the IRCC and the fact that the IRCC is not stored anywhere else than at the clinic. Thus, no patient consent will be requested for the data collection.

Discussion

The pilot study will be a crucial part of the EuMAR project, providing insight into the feasibility of collecting cumulative and prospective cycle-by-cycle data on MAR treatments from different European countries in a common registry. The findings of this study will guide

the decision on whether to move forward with the implementation of the registry after the end of the three-year EU-funded project period and feed into the policy recommendations that will be developed at the end of the project. If it is decided to implement the EuMAR registry after the project period, the information gathered will be valuable to support a smooth implementation.

Despite the anticipated important contribution of the EuMAR pilot study, several limitations need to be considered. Firstly, the study has a relatively short follow-up period of up to six months, which limits the possibility to test the collection of cumulative data, particularly in the context of cross-border and cross-institutional follow-up. It is unlikely that a significant number of patients will switch clinics within the same country during the study period and the case that a patient who initiated treatment in one pilot country switches to a clinic in another pilot country before the end of the study period is expected to occur very rarely if at all. Furthermore, even if a patient moves to another clinic during the pilot study, there are no means of assessing whether a ClinicSwitch code was in fact requested, since the anonymisation system makes it impossible to see whether a patient who does not present a ClinicSwitch code has previously had treatment at a different clinic and was already registered with a different IRCC. Another limitation of the pilot study is the lack of data sources for external comparison. This is in the nature of a project like EuMAR, which aims to build a data collection that is not yet existing. However, the accuracy of the data is expected to be high, since it will mostly be collected through automatic links with EMR systems or national registries.

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Annex 1 EuMAR parameters and definitions

Part 1: Parameters to be included in the register

Validation crosslink: none
Definition:
The centre code will need to be defined by the system and will also be used to be connected to the login for benchmarking.
The identification code for the centers will include the country.
A center list per country will be provided to allow selecting specific centers per region or category.

Module 1 - Identification

1. EuMAR IRCC

Definition:
Each individual will be defined in EuMAR through an Individual Reproductive Care Code (IRCC). The IRCC will be created automatically by the registry. The code will stay with the individuals as long as treatments are continued at the same center. If the individual moves to another center, a new IRCC will be created but it will be linked to the same individual in the background.

2. Cycle identification

a. FRESH cycle with own gametes
b. FRESH cycle with donated gametes
c. Frozen-thawed embryo transfer (FET) cycle with own gametes
d. Frozen-thawed embryo transfer (FET) cycle with gamete/embryo donation
e. Intra-uterine insemination (IUI) with partner gametes
f. Intra-uterine insemination (IUI) with donor gametes
g. Fertility Preservation (FP)

Definitions:
FRESH cycle: A MAR procedure in which cycle monitoring is carried out with the intention of transferring to a woman fresh embryo(s)/blastocyst(s). or cryopreserving all oocytes/embryos (adapted def IG)

Frozen-thawed embryo transfer (FET) cycles : An ART procedure in which cycle monitoring is carried out with the intention of transferring to a woman, frozen/thawed or vitrified/warmed embryo(s)/blastocyst(s). Note: A FET cycle is initiated when specific medication is provided or cycle monitoring is started in the female recipient with the intention to transfer an embryo (IG)

Intra-uterine insemination (IUI): A procedure in which laboratory processed sperm are placed in the uterus (in the ovulatory stage of the cycle) to attempt a pregnancy. (IG)

Fertility Preservation (FP): Various interventions, procedures and technologies, including cryopreservation of gametes, embryos or ovarian and testicular tissue to preserve reproductive capacity. (IG)

Module 2 – Patient variables

3. Country of current residence[1]

Definition:
Residence: The place where one actually lives, which may be different from one's domicile.
(https://www.law.cornell.edu/wex/residence#:~:text=1.,to%20residents%20of%20the%20state.)

4. Female Date of Birth

Definition:
The date of birth for the person undergoing the treatment (IUI, OPU, ovarian tissue collection, ET,...)

5. Female Body Mass Index (BMI)

Definition:
Body Mass Index (BMI) is a person's weight in kilograms (or pounds) divided by the square of height in meters (or feet). (https://www.cdc.gov/healthyweight/assessing/bmi/index.html)

6. Female current smoking status

a. Yes
b. No
c. Unknown

Definition:
A recoded variable based on several questions about cigarette smoking

7. Male Date of Birth

Definition:

[1] https://www.iso.org/iso-3166-country-codes.html

The day of birth for the male undergoing the ejaculated or surgically retrieved sperm collection.

8. Male Body Mass Index (BMI)

Definition:
Body Mass Index (BMI) is a person's weight in kilograms (or pounds) divided by the square of height in meters (or feet). (https://www.cdc.gov/healthyweight/assessing/bmi/index.html)

9. Male current smoking status

a. Yes
b. No
c. Unknown

Definition:
A recoded variable based on several questions about cigarette smoking

10. Indication for treatment

a. Female
    a. Unexplained infertility
    b. Tubal pathology
    c. Ovulatory disorder
    d. Endometriosis
    e. Psychosexual (can be an indication for IUI and occasionally IVF)
    f. Premature Ovarian Insufficiency (POI)/oocyte issue (these are women who need donor eggs)
    g. Uterine absence or dysfunction (female who needs surrogacy)
    h. Medical contraindication to pregnancy (surrogacy for medical disorders)
    i. Other

b. Male
    a. Unexplained
    b. Sperm factor
    c. Psychosexual (can be an indication for IUI and occasionally IVF)
    d. Other

c. Relationship status
    a. No male partner (same-sex or single women)
    b. No female partner (same-sex or single males)

d. Genetic reasons
    a. Genetic disorder (Need Preimplantation Genetic Testing - PGT)

Definitions:
Unexplained infertility: Infertility in couples with apparently normal ovarian function, Fallopian tubes, uterus, cervix and pelvis and with adequate coital frequency; and apparently normal testicular function, genito-urinary anatomy and a normal ejaculate. The potential for this diagnosis is dependent upon the methodologies used and/ or those methodologies available (IG)

Tubal pathology: Tubal abnormality resulting in dysfunction of the Fallopian tube, including partial or total obstruction of one or both tubes (proximally, distally or combined), hydrosalpinx and/or peri-tubal and/or peri-ovarian adhesions affecting the normal ovum pick-up function. It usually occurs after pelvic inflammatory disease or pelvic surgery. Tubal disease due to endometric adhesions is classed as endometriosis. (IG)

Ovulatory disorder: a group of disorders in which ovulation fails to occur, or occurs on an infrequent or irregular basis.
Shadygrovefertility.com/infertility-causes/ovulatory-disorder
PCOS guideline ?

Endometriosis: A disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium and myometrium. Intrapelvic endometriosis can be located superficially on the peritoneum (peritoneal endometriosis), can extend 5 mm or more beneath the peritoneum (deep endometriosis) or can be present as an ovarian endometriotic cyst (endometrioma) (IG)
Guidelines

Psychosexual (can be an indication for IUI and occasionally IVF):

Premature Ovarian Insufficiency (POI): A condition characterized by hypergonadotropic hypogonadism in women younger than age 40 years (also known as premature or primary ovarian failure). It includes women with premature menopause.

Uterine absence or dysfunction (female who needs surrogacy - males needing surrogacy): congenital anomalies, adenomyosis,…

Medical contraindication to pregnancy (surrogacy for medical disorders eg severe renal disease, heart disease, Turner syndrome,…)

Genetic disorder (Need PGT-M or PGT-SR): An inherited medical condition caused by a DNA abnormality.

Surrogacy: gestational carrier

Module 3 – Cycles with ovarian stimulation (If 2a, 2b, 2e, 2f, possibly 2g)

11. Ovarian stimulation

a. Yes
b. No

Definition:
Pharmacological treatment with the intention of inducing the development of ovarian follicles. It can be used for two purposes in ART, to obtain multiple oocytes at follicular aspiration. (IG)

12. Date of start cycle

Definition:
first day of menstruation when no ovarian stimulation is used and first day of drug when ovarian stimulation is used
This date is important to define time-to-pregnancy, but also to at least have a date in case of cancellation.

13. Treatment Protocol

Pre-Treatment

a. None
b. Oestrogen
c. Progestogen
d. Oestrogen progestogen (OCP)
e. Gonadotrophin Releasing hormone (GnRH) antagonist
f. Other

LH Suppression Protocol

a. None
b. GnRH Agonist
c. GnRH Antagonist
d. Progestagen
e. Other

Stimulation Drug

a. None (Natural cycle)Modified natural cycle
b. Oral agent only (Anti-oestrogen, Aromatase Inhibitor)

c. Oral agent and gonadotropin
d. Gonadotropin only

Gonadotropin (if used)
a. Urinary
b. Recombinant
c. Urinary and Recombinant

Starting dose of Gonadotropin (if used)
a. <150 IU
b. 150-300 IU
c. >300 IU

Triggering of final oocyte maturation
a. Human chorionic gonadotropin (hCG) urinary
b. hCG recombinant
c. GnRH Agonist
d. Dual trigger (hCG and GnRH agonist)
e. Other

Luteal support
a. None
b. hCG
c. Progesterone
d. Other Progestogenes
e. Combination

Luteal support prescribed until
a. Pregnancy test
b. Viability scan (6-8 weeks)
c. End of first trimester

Other

14. Cancellation prior to Ovum Pick Up (OPU)

a. Yes
b. No

Definition: Cycle that was abandoned before OPU, at the stimulation stage

15. OPU Cancellation causes

a. Insufficient ovarian response
b. Premature Luteinizing Hormone (LH)

c. Other medical reasons
d. Non-medical reason

Definition:
Insufficient ovarian response: Recruitment of a low number of follicles, fewer than expected and/or considered clinically possible

Premature Luteinizing Hormone: Conventionally, premature LH surge is defined as an LH level of ≥ 10 mIU/mL, and a progesterone level of ≥1.0 ng/mL occurring before the criteria of hCG administration is met

OHSS: An exaggerated systemic response to ovarian stimulation characterized by a wide spectrum of clinical and laboratory manifestations. It may be classified as mild, moderate or severe according to the degree of abdominal distention, ovarian enlargement and respiratory, hemodynamic and metabolic complications (IG)

16. Date of OPU

Definition : The date when ovum pick up (OPU) occurred.

17. Number of cumulus oocytes retrieved

Definition: The number of cumulus oocytes retrieved at OPU

18. In-vitro maturation (IVM)

a. Yes
b. No

Definition:
A cycle is considered an IVM cycle if the patient was prepared specifically or if an alternate treatment cycle was converted prior to OPU into an IVM treatment cycle

19. Number of oocytes cryopreserved

Definition:
The number of oocytes frozen before fertilization

20. Reasons for oocyte cryopreservation

a. Medical reason
   - OHSS risk
   - Infection

- Intercurrent disease
- Sperm issues
- Fertility preservation (Polyp/endometrial issue)
- other

b. Non-medical reason
- Religion
- Legal issues
- Planned autologous egg banking (fertility preservation)
- Other

c. Donation

Definition:
Cryopreservation: The process of slow freezing or vitrification to preserve biological material (e.g. gametes, zygotes, cleavage-stage embryos, blastocysts or gonadal tissue) at extreme low temperature. (IG)
Intercurrent disease: A disease that intervenes during the course of another disease. For instance a patient with AIDS may develop an intercurrent bout of pneumonia.

21. Number of oocytes donated

Definition: The number of oocytes given by the patient for reproductive purposes of others or for research (adapted from IG)

Module 4 – Laboratory data

22. Source of sperm:

a. Origin
1. Partner sperm (own sperm)
2. Donor sperm

b. Collection
1. Ejaculation
2. Retrograde ejaculation
3. Surgical retrieval
4. Combination of ejaculation and surgical retreival

c. Type of sperm
1. Fresh
2. Frozen
3. Combination of fresh and frozen

Definition:
Ejaculated sperm: sperm cells released from the male reproductive system
Antegrade ejaculation: Normal, forward ejaculation

Retrograde ejaculation: The complete or partial inability to ejaculate in an antegrade direction

23. Source of oocytes

a. Origin
    1. Own oocytes
    2. Donor oocytes (age of donor at time of oocytes collection)
b. Type of oocytes
    1. Fresh
    2. Frozen
    3. Combination of fresh and frozen

Definition: /

24. Date of insemination

Definition: Date when sperm and oocyte are brought together

25. Insemination technique used:

a. IVF
b. ICSI
c. Mixed IVF and ICSI
d. IUI

26. Number of oocytes inseminated (IVF)

Definition: Number of oocytes in which a sperm cell has entered

27. Number of oocytes injected (ICSI)

Definition: Number of oocytes in which a sperm cell was injected

28. Number of 2 pronuclei (2pn) – IVF

Definition:
Pronucleus: A round structure in the oocyte surrounded by a membrane containing chromatin. Normally, two pronuclei are seen after fertilization, each containing a haploid set of chromosomes, one set from the oocyte and one from the sperm, before zygote formation (IG)

29. Number of pronuclei (2pn) – ICSI

Definition:

Pronucleus: A round structure in the oocyte surrounded by a membrane containing chromatin. Normally, two pronuclei are seen after fertilization, each containing a haploid set of chromosomes, one set from the oocyte and one from the sperm, before zygote formation (IG)

30. Number of all embryos developed (IVF and ICSI)

31. Number of embryos cryopreserved

32. Optional: Number of cleavage stage embryos cryopreserved

Definition:
Cleavage stage embryo: Embryos beginning with the 2-cell stage and up to, but not including, the morula stage

33. Optional: Number of blastocysts cryopreserved

Definition:
Blastocyst: The stage of preimplantation embryo development that occurs around day 5–6 after insemination or ICSI. The blastocyst contains a fluid-filled central cavity (blastocoele), an outer layer of cells (trophectoderm) and an inner group of cells (inner cell mass).

34. Reasons for embryo cryopreservation

a. Supernumerary embryos
b. PGT
c. Medical reason
    - OHSS risk
    - Infection
    - Intercurrent disease
    - Fertility preservation
    - Uterine or tubal pathology undiagnosed before cycle start
    - other
d. Non-medical reason
    - Religion
    - Legal issues
    - other
e. Planned freeze all) for autologous use /fertility preservation)
f. Donation

35. Pre-implantation Genetic Testing

a. No

b. Yes

If yes,

- PGT-A
- PGT-M
- PGT-SR

Definition:

Preimplantation Genetic Testing: A test performed to analyze the DNA from oocytes (polar bodies) or embryos (cleavage stage or blastocyst) for HLA-typing or for determining genetic abnormalities. These include: PGT for aneuploidies (PGT-A); PGT for monogenic/single gene defects (PGT-M); and PGT for chromosomal structural rearrangements (PGT-SR).

Module 5 – Embryo transfer

Make choice between (fresh/thawed)

36. Embryo transfer:

a. Yes
b. No

Definition:

Placement into the uterus of an embryo at any embryonic stage from day 1 to day 7 after IVF or ICSI.

37. Embryo transfer of:

a. Fresh embryos
b. Frozen embryos
c. Combination of fresh and frozen embryos

Use of fresh embryos

38. Date of embryo transfer

Definition:

Date on which the embryos are transferred to the uterus

39. Number of cleavage stage embryos transferred.

40. Number of blastocysts transferred.

41. Embryo Transfer Outcome

a. HCG detected (Positive Pregnancy test)

b. No HCG detected (Negative pregnancy test)
c. Lost to follow-up

Use of frozen embryos

42. Date of thawing

Definition:
Thawing: The process of raising the temperature from the storage temperature to room/physiological temperature (adapted from IG)
Date of thawing: date on which the frozen embryos are taken out of the storage and container

43. Frozen Embryo Transfer protocol (FET)

a. natural cycle (NC) - no medication
b. modified NC (only HcG trigger)
c. hormone replacement cycle (estrogen-progesterone)
d. stimulated cycle (stimulated with gonadotrophins, aromase inhibitors, SERMs)

Definition:
Natural cycle: A menstrual cycle without the use of any pharmacological compound.
Modified NC: A spontaneous menstrual cycle in which pharmacological compounds are administered with the sole purpose of inducing timed ovulation

44. Luteal support in FET:

a. None
b. hCG
c. Progesterone
d. Combination

Definition:
Luteal support: Hormonal supplementation in the luteal phase, usually progesterone.

45. Date of embryo transfer (link to OPU if available)

46. Number of cleavage stage embryos transferred.

47. Number of blastocysts transferred.

48. Embryo Transfer Outcome

a. HCG detected (Positive Pregnancy test)

b. No HCG detected (Negative pregnancy test)
c. Lost to follow-up

General

49. Cause of no embryo transfer

a. No embryos (failed fertilization/failed cleavage)
b. No embryos (failed thawing)
c. PGT
d. Medical reason
   - OHSS risk
   - Infection
   - Intercurrent disease
   - other
e. Non-medical reason
   - Religion
   - Legal issues
   - Other
f. Autologous use (planned freeze all)
g. Fertility preservation
h. Donation
i. Other

Module 6 – Complications during pregnancy

To be completed if 41a and/or 48a

Definition Pregnancy: A state of reproduction beginning with implantation of an embryo and ending with the complete expulsion and/or extraction of all products of implantation

50. Complications

a. Yes
b. No
c. Unknown

Definition:

Complications of pregnancy include physical and mental conditions that affect the health of the pregnant or postpartum person, their baby, or both. Physical and mental conditions that can lead to complications may start before, during, or after pregnancy

51. Causes of complications

a. OHSS Severe (Grade III – IV or hospitalization for lesser grades)
b. Infection (Pelvic Inflammatory Disease - PID)

c. Bleeding requiring hospitalization, blood transfusion and/or surgery
d. Thrombosis
   Within 6 weeks after delivery
e. Maternal Death, assumed to be linked to ART/IUI cycle
   Within 6 weeks after delivery
f. Maternal Death, link with treatment cycle not established
   Within 6 weeks after delivery??
g. Other

Definition:

OHSS: To be reported: Grade 3, Abdominal distension and discomfort (grade 1) plus nausea, vomiting, and/or diarrhea, ovaries 5-12cm plus ultrasonic evidence of ascites (grade 3); Grade 4, Grade 3 + clinical evidence of ascites and/or hydrothorax or dyspnoea; Grade 5, All above plus haemoconcentration, coagulation abnormalities, diminished renal perfusion (EIM)

Pelvic Inflammatory disease: an infection of the female reproductive organs. It most often occurs when sexually transmitted bacteria spread from your vagina to your uterus, fallopian tubes or ovaries.

Thrombosis: A blood clot in the deep vein (also known as a deep vein thrombosis or DVT) is a medical condition that typically occurs in the lower leg, thigh, pelvis or arm. When a DVT is left untreated, a part of the clot can break off and travel to the lungs, causing a blockage called a pulmonary embolism (PE).

Module 7 – Pregnancy and outcome

To be completed if 41a and/or 48a

52. Number of intra-uterine gestational sacs on ultrasound scan

Definition:

Clinical pregnancy: A pregnancy diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy. In addition to intra-uterine pregnancy, it includes a clinically documented ectopic pregnancy

Gestational sac: A fluid-filled structure associated with early pregnancy, which may be located inside or, in the case of an ectopic pregnancy, outside the uterus.

53. Details of twin pregnancy

a. Monoamniotic
b. Diamniotic
    a. Monochorionic
    b. Dichorionic

Definition:

Monoamniotic: occur when a single fertilized ovum (egg) results in identical twins that share a common placenta and amniotic sac.

Diamniotic: twin pregnancy with two distinct amniotic cavities.

Monochronic: a form of multiple gestation in which each twin shares a placenta but has its own amniotic sac

Dichronic: a form of multiple gestation in which each twin has a separate placenta and amniotic sac

54. Fetal reductions

a. Yes
b. No

Definition:

a first-trimester or early second-trimester procedure for reducing the total number of fetuses in a multifetal pregnancy.

55. Clinical pregnancy outcome

a. Delivery after 22 weeks
b. Ectopic pregnancy
c. First-trimester miscarriage
d. Second-trimester miscarriage
e. Induced abortion
        Reason?
f. Molar pregnancy
g. Loss of follow-up

Definition:

Ectopic pregnancy: A pregnancy outside the uterine cavity, diagnosed by ultrasound, surgical visualization or histopathology. (IG)
Miscarriage: the spontaneous or unplanned expulsion of a fetus from the womb before it can survive independently.
Induced abortion: Intentional loss of an intrauterine pregnancy, through intervention by medical, surgical or unspecified means. (
Molar pregnancy: uncommon abnormal type of pregnancy in which a non-viable fertilized egg implants in the uterus
Loss of follow-up: refers to pregnant patients who at one point in time were actively followed, but have become lost at the point of follow-up of the pregnancy.

56. Date of delivery

Definition:
Delivery: The complete expulsion or extraction from a woman of one or more fetuses, after at least 22 completed weeks of gestational age, irrespective of whether they are live births or stillbirths. A delivery of either a single or multiple newborn is considered as one delivery. If more than one newborn is delivered, it is often recognized as a delivery with multiple births
Date of delivery: date on which the child(ren) is/are born

57. N of children born

58. Number of stillbirths

Definition:
Stillbirth: The death of a fetus prior to the complete expulsion or extraction from its mother after 22 completed weeks of gestational age. The death is determined by the fact that, after such separation, the fetus does not breathe or show any other evidence of life, such as heartbeat, umbilical cord pulsation, or definite movement of voluntary muscles. Note: It includes deaths occurring during labor

Liveborn Child 1

59. Sex

a. *Male*
b. *Female*
c. Unknown or undetermined

60. Birth weight

Definition:
Weight of the newborn at birth

61. Neonatal outcome

a. Routine postnatal care
b. Admission to neonatal special care unit

Definition:
Neonatal: The period which commences at birth and ends at 28 completed days after birth.

62. Neonatal malformations

a. Yes
b. No
c. Unknown

Definition:
Alterations in the structure and function of the organ systems of a newborn that occurs in intrauterine life and is identified before, at, or later after birth. All birth defects according to ICD 10 Q codes are reported by the IVF units. Later, be sorted centrally for major and minor birth defects. See : European Concerted Action on Congenital Anomalies and Twins (EUROCAT) (https://eu-rd-platform.jrc.ec.europa.eu/eurocat/data-collection/guidelines-for-data-registration_en) for classification in major and minor.

Questions on children for every liveborn child
Child 2
Child 3

Module 8 - IUI

Parameters 3/4/5/6/7/8/9/10/13/22/24/25/

- Indications (10) but without POI, surrogacy cases, PGT**,** tubal pathology
- If 25 = IUI
  ⇨ New questions
- Was IUI cancelled:
  a. Yes
  b. No

If yes: reason

If no: outcome
- HCG detected (Positive Pregnancy test)
- No HCG detected (Negative pregnancy test)
- Lost to follow-up

Link to complications and pregnancy

Module 9 – Fertility preservation

63. Method of fertility preservation:

a. Pre-pubertal ovarian tissue collection and cryopreservation
b. Post-pubertal ovarian tissue collection and cryopreservation
c. Oocyte cryopreservation
d. Pre-pubertal testicular tissue collection and cryopreservation
e. Post-pubertal testicular tissue collection and cryopreservation
f. Ejaculated sperm collection and cryopreservation
g. Epididymal/testicular sperm collection and cryopreservation

64. Reason for fertility preservation

a. Medical
    2. Oncology
    3. Benign medical conditions (eg endometriosis, benign haematological disorders in children,..)
    4. Gender reassignment
    5. Differences in Sex Development (DSD)
    6. Surgical risk for later infertility
b. Non-medical
    1. Prior to vasectomy
    2. Personal patient linked reason (planned egg banking, social sperm freezing,…)

Definition:
Fertility preservation: Various interventions, procedures and technologies, including cryopreservation of gametes, embryos or ovarian and testicular tissue to preserve reproductive capacity.
Gender reassignment: the process (typically involving a combination of surgical procedures and hormone treatment) undertaken by a transgender person to alter their physical sexual characteristics to match their gender identity.
DSD: is a group of rare conditions involving genes, hormones and reproductive organs, including genitals. It means a person's sex development is different to most other people's.

Freeze-all cycles

- ICMART definition for freeze-all : An ART cycle in which, after oocyte aspiration, all oocytes and/or embryos are cryopreserved and no oocytes and/or embryos are transferred to a woman in that cycle.

- For reporting, it may make more sense to report the deliveries per first ET (fresh or frozen) – as this will discriminate between couples with only one embryo going for fresh transfer, and better prognosis patients that will have several frozen cycles.

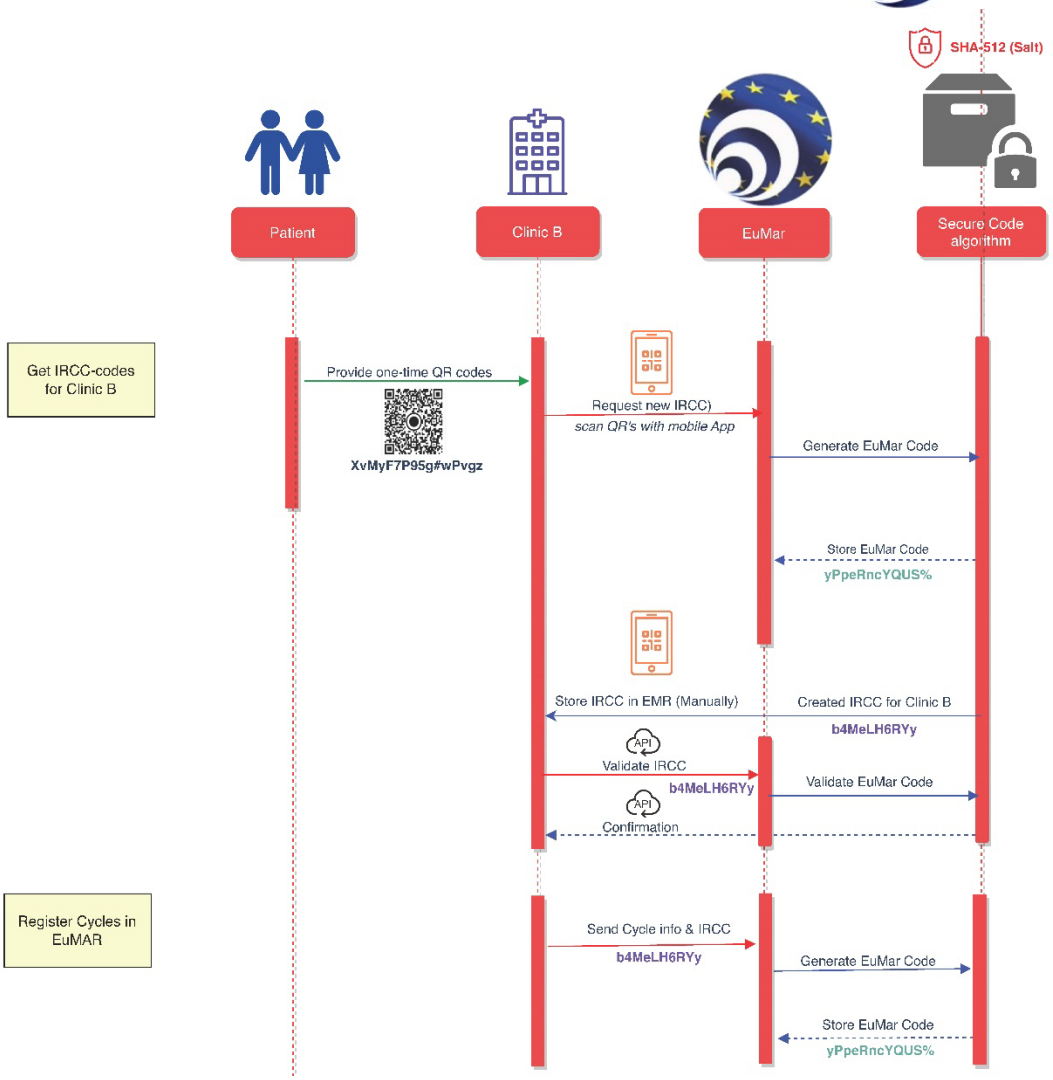
Part 2: Parameters to be derived from the register

Parameter	Definition
# of treated individuals	# of individual persons that had at least one treatment cycle intervention (IUI, IVF/ICSI and/or FET) completed
Age of the individual	Date of start cycle minus date of birth
# of couples that had at least one treatment cycle intervention (IUI, IVF/ICSI and/or FET) completed	# of couples that had at least one treatment cycle intervention (IUI, IVF/ICSI and/or FET) completed
# of treatment cycles without stimulation	# of cycles without ovarian stimulation (includes hormone substituted cycles) that ended up with one of the interventions
# of treatment cycles with stimulation (subdivided IVF/ICSI/ED/IUI/FERTIL PRESERV)	# of cycles with ovarian stimulation (excludes hormone substituted cycles) that ended up with one of the interventions
# of oocyte retrievals (subdivided)	# of retrieval procedures where at least one oocyte was retrieved
# of oocytes retrieved (subdivided)	# of oocytes retrieved in total
# of oocytes cryopreserved (subdivided)	# oocytes cryopreserved in total
# of embryos cryopreserved	# of embryos
# of cleavage stage embryos cryopreserved	# of embryos
# of blastocysts cryopreserved	# of embryos
# of embryo transfers (fresh or cryo)	# of procedures, regardless of the number of embryos transferred
# of single embryo transfers (fresh or cryo)	# of procedures, with only one embryo transferred

# of double embryo transfers (fresh or cryo)	# of procedures, with two embryo transferred
# of deliveries	# of deliveries regardless of the number of children born (including stillborn)
# of live born children	# of infants with any vital signs
Distribution fresh embryo transfers/FET	# of fresh cycles x100/ Total fresh +FET cycles or # of FET cycles x100/ Total fresh +FET cycles
Distribution IVF/ICSI	# of IVF cycles x100/ Total IVF+ICSI cycles or # of ICSI cycles x100/ Total IVF+ICSI cycles
ART infants per national births	# of children born from ART x100/total number of children born in a specific country
Size of the clinics	# of treatment cycles performed in one year
Cycles per million inhabitants	# treatment cycles/million inhabitants in a specific country
Cycles per million females of reproductive age	# treatment cycles/million females of reproductive age (15-45 years)in a specific country
Cycle cancellation rate (before OPU) (%CCR)	Nr of cycles cancelled before OPU × 100 / Nr of started cycles
Rate of cycles with moderate/severe OHSS (% OHSS)	Nr of cycles with moderate to severe OHSS × 100 / Nr of started cycles
Complication rate after OPU other than OHSS (%CoOPU)	Nr of complications (any) that require an (additional) medical intervention or hospital admission (apart from OHSS) × 100 / Nr of OPUs performed
Clinical pregnancy rate (%CPR) (Per transfer + subdivided per treatment)	Nr of pregnancies (diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy) × 100 / Nr of embryo transfer cycles

Clinical pregnancy rates per transfer (per age category) (subdivided)	Nr of pregnancies (diagnosed by ultrasonographic visualization of one or more gestational sacs or definitive clinical signs of pregnancy) × 100 / Nr of embryo transfer cycles per age category
Multiple pregnancy rate (%MPR) (proportion twin-triplet? + subdivided)	Nr of pregnancies with more than one embryo or foetus × 100 / Nr of pregnancies
Delivery rate (per transfer) % (and per aspiration? + subdivided)	Nr of deliveries × 100 / Nr of transfers
Delivery rate per age category (subdivided)	Nr of deliveries in specific age group × 100 / Nr of transfers in the same age group
Multiple delivery rate (%MDR) (proportion of all + subdivided by number of fetuses)	Nr of deliveries with more than one foetus × 100 / Nr of deliveries
Cumulative pregnancy rate	The number of oocyte retrievals resulting in at least 1 clinical pregnancy within 1 year of the oocyte retrieval cycle divided by the total number of oocyte retrieval cycles that had at least 1 fresh or frozen embryo transfer.
Cumulative delivery rate	The cumulative delivery rate (CDR) per initiated/aspiration cycle after the transfer of all fresh and frozen–thawed/warmed embryos has been suggested to be the critical endpoint that sets these groups apart
Term of the pregnancy at birth : a. at term b. preterm < 37 weeks c. very preterm < 28 weeks	Number of weeks since the day of OPU/FET/IUI plus 2.

Annex 2 IRCC concept flows


SHA-512 (Salt)
Patient
Clinic B
EuMar
Secure Code algorithm
Get IRCC-codes for Clinic B
Provide one-time QR codes
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Request new IRCC)
scan QR's with mobile App
Generate EuMar Code
Store EuMar Code
yPpeRncYQUS%
Store IRCC in EMR (Manually)
Created IRCC for Clinic B
b4MeLH6RYy
API
Validate IRCC
b4MeLH6RYy
Validate EuMar Code
API
Confirmation
Register Cycles in EuMAR
Send Cycle info & IRCC
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Generate EuMar Code
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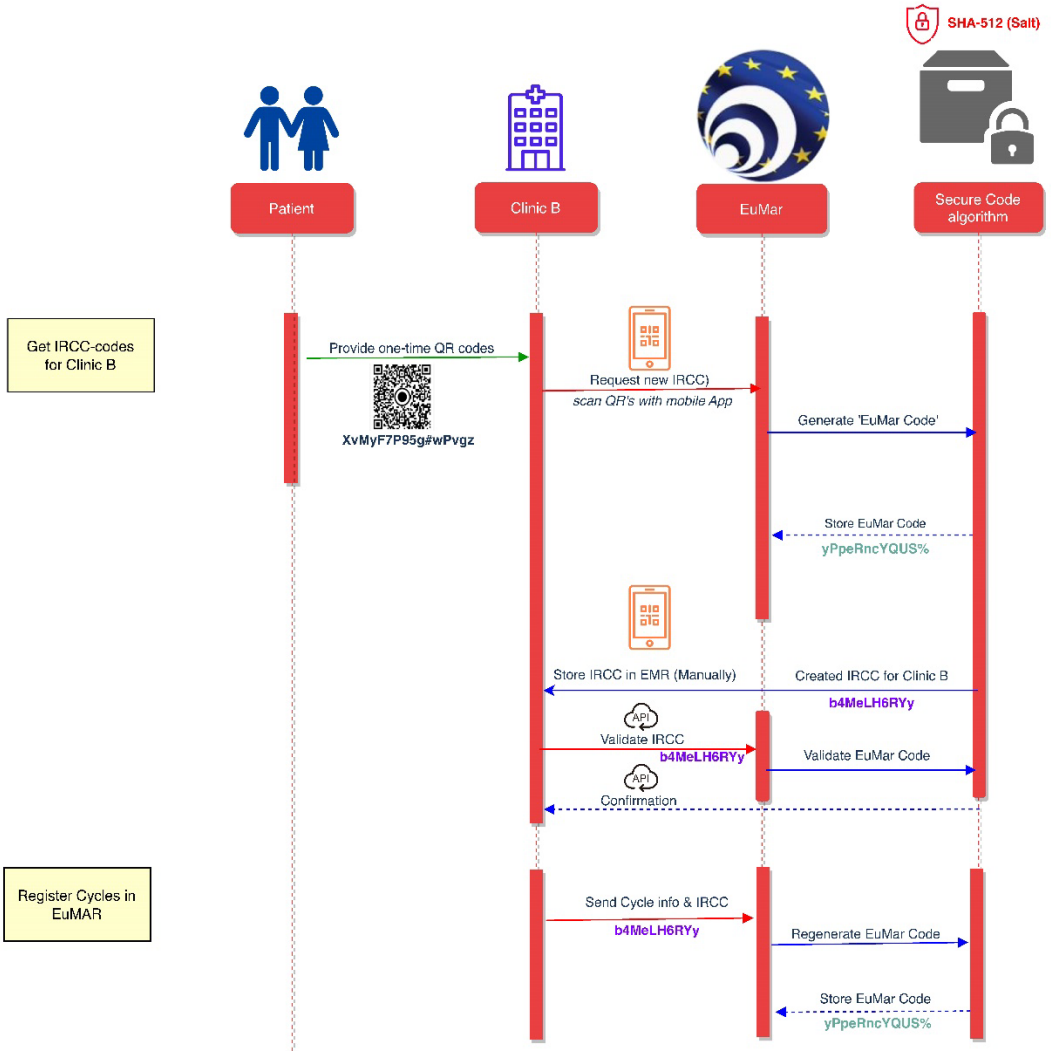
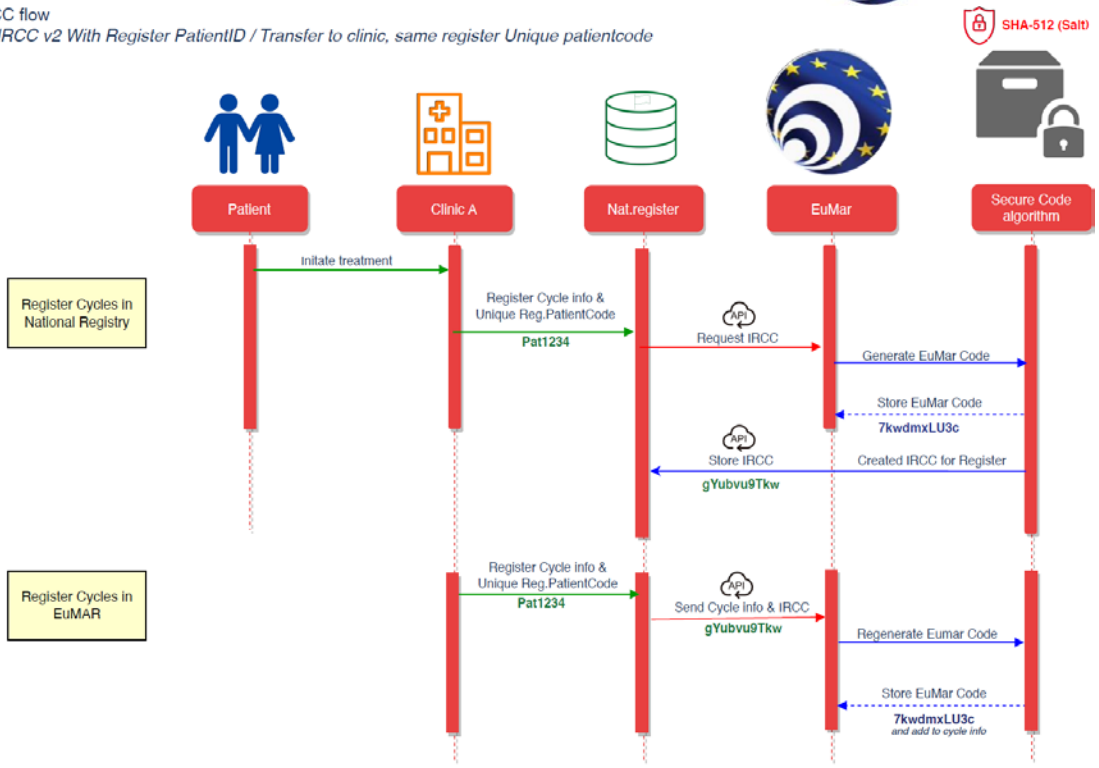
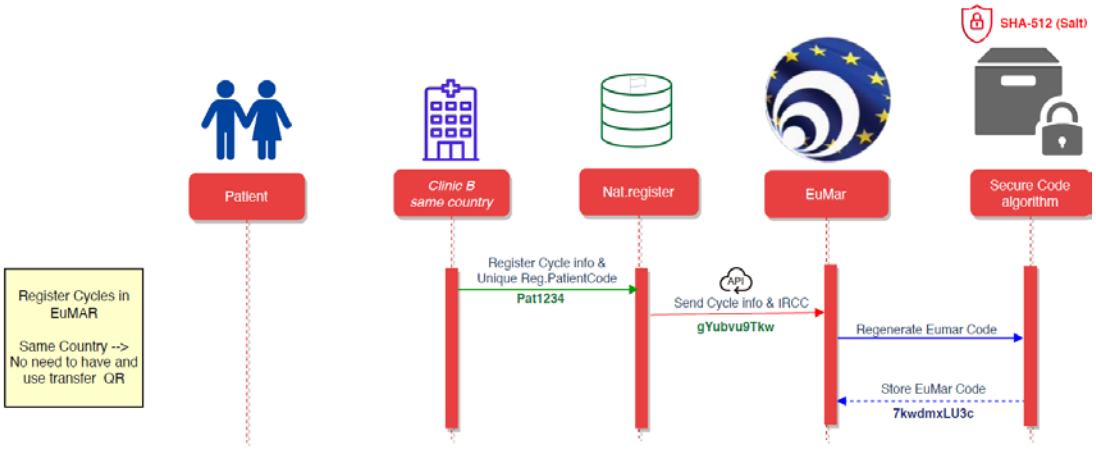
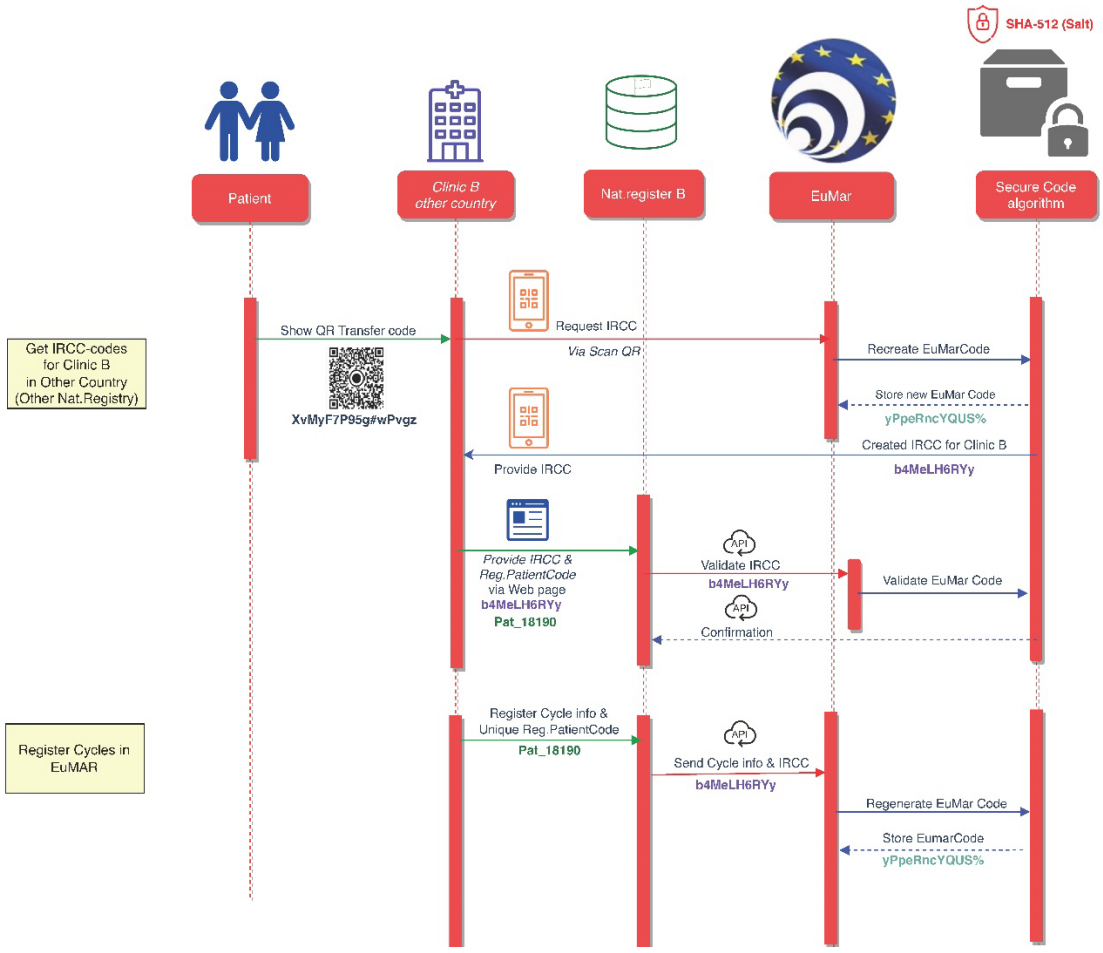

SHA-512 (Salt)
Patient
Clinic B
EuMar
Secure Code algorithm
Get IRCC-codes for Clinic B
Provide one-time QR codes
XvMyF7P95g#wPvgz
Request new IRCC)
scan QR's with mobile App
Generate 'EuMar Code'
Store EuMar Code
yPpeRncYQUS%
Store IRCC in EMR (Manually)
Created IRCC for Clinic B
b4MeLH6RYy
API
Validate IRCC
b4MeLH6RYy
Validate EuMar Code
API
Confirmation
Register Cycles in EuMAR
Send Cycle info & IRCC
b4MeLH6RYy
Regenerate EuMar Code
Store EuMar Code
yPpeRncYQUS%

EuMAR - IRCC flow

2.b. EuMAR IRCC v2 With Register PatientID / Transfer to clinic, same register Unique patientcode in Register






SHA-512 (Salt)
Patient
Clinic B
other country
Nat register B
EuMar
Secure Code
algorithm
Get IRCC-codes
for Clinic B
in Other Country
(Other Nat.Registry)
Show QR Transfer code
XvMyF7P95g#wPvgz
Request IRCC
Via Scan QR
Recreate EuMarCode
Store new EuMar Code
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Created IRCC for Clinic B
b4MeLH6RYy
Provide IRCC
Provide IRCC &
Reg.PatientCode
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b4MeLH6RYy
Pat_18190
Validate IRCC
b4MeLH6RYy
Validate EuMar Code
Confirmation
Register Cycles in
EuMAR
Register Cycle info &
Unique Reg.PatientCode
Pat_18190
Send Cycle info & IRCC
b4MeLH6RYy
Regenerate EuMar Code
Store EumarCode
yPpeRncYQUS%

EuMAR - IRCC flow

2.d. EuMAR IRCC v2 with Register NO PatientID