EuMAR by ESHRE

European monitoring of Medically Assisted Reproduction (EuMAR)

D 4.1 Characteristics and parameters with accepted terminology

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Table of Contents

Index of Figures and Tables

Acronyms and abbreviations

ART	Assisted Reproductive Technology
D	Deliverable
DG SANTE	Directorate General For Health and Food Safety
EDQM	European Directorate for the Quality of Medicines & HealthCare
EIM	European IVF Monitoring
ESHRE	European Society of Human Reproduction and Embryology
EU	European Union
EuAC	European Affairs Committee
GDPR	General Data Protection Regulation
HaDEA	European Health and Digital Executive Agency
ICMART	International Committee for Monitoring Assisted Reproductive Technologies
IRCC	Individual Reproductive care code
IT	Information Technology
IUI	Intra Uterine Insemination
IVF	In Vitro Fertilisation
MAR	Medically Assisted Reproduction
PSC	Project Steering Committee
SARE	Serious Adverse Reactions and Events
WP	Work Package

Authors

This report was written by the members of WP4 (Table 1).

Table 1: Work Package 4 members

WP member	*Function*
Christina Bergh	Member of EIM steering committee
Roberto De Luca	Member of EIM steering committee
Mika Gissler	Member of EIM Consortium
Borut Kovacic	EuAC
Mary Wingfield	Member of EIM Consortium
Janos Urbancsek	Member of EIM Consortium
Susanne Hultsch	WP support
Nathalie Vermeulen	WP support
Veerle Goossens	WP support and EIM support
Jesper Smeenk	WP-Leader and EIM chair

Executive Summary

EuMAR aims to establish a pan-European registry for comprehensive MAR data, addressing the need for transparency and biovigilance. Its objectives include a tailored data flow model, a glossary of standardised parameters and an IT solution for data collection. Integral to EuMAR, WP4 aligns with Project Objective 2, focusing on the identification and definition of key MAR parameters for cycle-by-cycle data collection.

In this report we detail the methodology employed to establish and finalise a foundational set of core parameters for the forthcoming IT solution intended for the EuMAR database. Additionally, we share the finalised parameter list crafted by the working group, which has been submitted to the stakeholders for their approval. Any input received during the approval phase will be integrated in early 2024 and subsequently shared with the IT company for further adjustments of the data registry.

The successful completion of WP4 contributes to a standardised glossary and MAR parameter framework, facilitating harmonisation and integration with existing registries. Stakeholder engagement ensures a comprehensive and inclusive approach.

Introduction

EuMAR Project Summary

EuMAR aims to develop a pan-European registry of prospective cycle-by-cycle data on the use and outcomes of MAR treatments. EuMAR addresses the need for more transparency, surveillance, and biovigilance in MAR across country borders, including better data on the safety of MAR for offspring, donors and recipients, in line with the revision of the EU Directives on blood, tissues and cells.

The ultimate goal of EuMAR is to provide the different stakeholders, including EU and national health authorities as well as the general public, with high quality data to quantify the effectiveness and safety of current and new technologies in MAR, including fertility preservation. To achieve this goal, EuMAR sets out to

i) develop a tailored data flow model that meets the national requirements of all EU Member States and avoids duplication of efforts;

ii) prepare a glossary of standardised parameters on which data is to be collected with corresponding definitions;

iii) develop an IT solution for data collection, including an "Individual Reproductive Care Code" (IRCC) that allows prospective data collection and cumulative follow-up across different centres/countries. The IT solution will be tested in a pilot study in five different EU Member States that will reflect the variations in current national data collection systems.

To maximise the value of the data collection for all stakeholders and to allow keeping up with future innovation and extended digitalisation, the EuMAR Registry will be developed with flexibility towards innovation and towards a future connection with existing national and international databases (interoperability).

In these activities, EuMAR can build on the existing network between the representatives of the health authorities of most EU Member States, as managed by the European IVF-Monitoring (EIM) consortium of the European Society of Human Reproduction and Embryology (ESHRE).

Work Package 4

WP4 is a crucial element of the EuMAR project, aligning with Project Objective 2 to identify and define key parameters in Medically Assisted Reproduction (MAR).

The overarching goal of WP4 is to develop a comprehensive understanding of relevant MAR parameters, encompassing patient and embryological characteristics, as well as treatment and outcome parameters. This understanding is crucial for prospective cycle-by-cycle data collection, especially in the context of the longitudinal EuMAR data collection, which incorporates cumulative outcome data analysis. Through this approach, WP4 aims to surpass the limitations of the current data collections.

WP4 is structured around 3 tasks:

1. Characteristics and Parameters with Accepted Terminology (T4.1):

Develops a list for comprehensive cycle-by-cycle data collection, considering MAR treatment cycles. Standard definitions are created with stakeholder input and endorsement is sought.

2. Characteristics and Parameters: Definition of Type, Format and Validation Conditions (T4.2):

Complements identified characteristics and parameters with data type, format and validation conditions for integration into the registry roadmap.

3. Characteristics and Parameters: Translation to Other Languages (T4.3):

Translates characteristics and parameters into national languages for EU Member States, ensuring accuracy through professional translation and verification.

Ultimately, the successful completion of WP4 will contribute to the establishment of a standardised glossary and framework for MAR parameters, facilitating proper data harmonisation and enabling seamless integration with existing registries. The engagement of stakeholders throughout the process ensures a comprehensive and inclusive approach to parameter identification and definition.

Parameters and Definitions

A list of characteristics (patient characteristics, embryological characteristics) and parameters (treatment parameters and outcome parameters) was defined to be included in the prospective cycle-by-cycle data collection. The list was drafted by the working group based on their profound knowledge of MAR treatment cycles and fertility preservation and was much extended for the longitudinal EuMAR data collection with cumulative outcome data analysis as compared to the current cross-sectional approach. Parameters were added to ensure relevant output parameters can be calculated for validation against EIM standardised data collection and to ensure continuation of the historical data collection. Finally, parameters were added to allow transfer of data to other existing registries, such as SARE and to make sure all aspects and possibilities of MAR and fertility preservation treatments are covered.

To define a standard definition for each characteristic and parameter, information was collected from currently accepted international terminology (ICMART), other published data, as well as definitions currently used in other registries. Some of the definitions were adapted or added through a consensus process among the working group.

Methodology

Creating a methodology to agree on a parameter list for a MAR-database involves a tailored approach sensitive to the specific requirements of reproductive medicine and patient data. During the first year of the EuMAR project, we developed the parameter list that will serve as basis for the IT development. For this, we used the following approach:

1. Multidisciplinary Team

For Work Package 4, responsible for the development of a list of core, standardised parameters with corresponding definitions on which data is to be collected, a multidisciplinary team including embryologists, doctors and data analysts were brought together (Table 1). This diverse group ensures comprehensive insight into medical, ethical and technical aspects.

2. Database Objectives and Regulatory Compliance

The objectives of the IVF database, including clinical, research and reporting purposes were clearly outlined. Alignment with relevant regulatory frameworks such as GDPR to address privacy and data security concerns were ensured.

3. Data Elements

During an in-person meeting, involving medical professionals, essential data elements were identified. These data included patient demographics, treatment protocols, laboratory procedures, embryology data, pregnancy outcomes and follow-up details where possible.

4. Prioritisation of Data Parameters

The data parameters based on their clinical significance, relevance for research and utility for reporting purposes were evaluated and prioritised. Critical fields necessary for successful follow-up, treatment outcomes and compliance were determined.

5. Data Model

A data model that organises the identified parameters logically was created and the relationships between different data elements to maintain consistency and integrity within the IVF database were evaluated.

6. Data Glossary

A comprehensive data glossary detailing each parameter and including descriptions, data types, allowable values, units of measurement and any constraints or dependencies was set up. This document serves as a reference for stakeholders.

7. Review and Validation

The proposed parameter list and data dictionary were shared with the members of the working group and the Project Steering Committee on several occasions during the process of defining and agreeing on all parameters and their definitions. The final agreed list was then shared with the stakeholders, being all National Competent Authorities, EDQM, DG SANTE, Fertility Europe (patient organisation), the EIM Consortium and ICMART, for review and validation. Feedback was incorporated and consensus among the team members regarding the finalised parameter list was ensured.

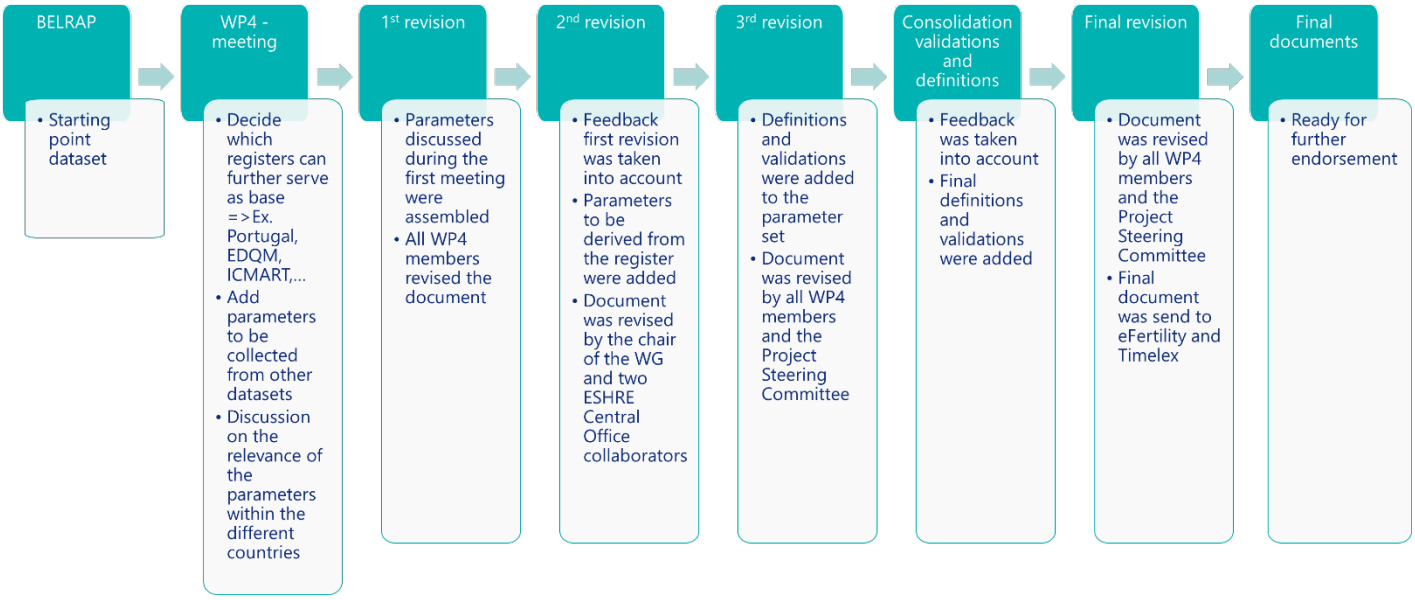

Figure 1: Decision making process

The parameters and definitions

A document was created that outlines nine modules encompassing 65 parameters complete with their respective definitions and anticipated validation processes.

The modules included were:

1. Identification

2. Patient variables

3. Cycles with ovarian stimulation

4. Laboratory data

5. Embryo data

6. Complications during pregnancy

7. Pregnancy and outcome

8. IUI

9. Fertility preservation

The complete list of parameters and definitions is added to this document as Annex 1.

Task 4.3 of Work Package 4 consists of translating the core parameter list into the different languages of the participating pilot countries. These translations will be provided once the decision and agreement on the pilot countries is confirmed.

Conclusion

In summary, within the EuMAR project, Work Package 4 plays a key role in creating a comprehensive list of standardised definitions for essential parameters of Medically Assisted Reproduction. This parameter list, which outlines nine modules encompasses 65 parameters, covering various aspects of MAR, from patient variables to fertility preservation and represents a crucial first step towards the establishment of a pan-European registry. The prospective cycle-by-cycle data generated by this effort will contribute to data harmonisation and transfer. In essence, WP4 marks a crucial milestone in enabling improved data collection, analysis and collaboration in Medically Assisted Reproduction.

References definitions parameters

[1] ESHRE Clinic PI Working Group, et al, The Maribor consensus: report of an expert meeting on the development of performance indicators for clinical practice in ART, *Human Reproduction Open*, Volume 2021, Issue 3, 2021, hoab022, https://doi.org/10.1093/hropen/hoab022

[2] https://www.edqm.eu/en/d/162521?p_l_back_url=%2Fen%2Fsearch%3Fq%3Dactivity%2Bdata%2Bmar

[3] https://www.icmartivf.org/glossary

[4] Helena Teede et al. (full authorship above). International Evidence-based Guideline for the Assessment and Management of Polycystic Ovary Syndrome 2023. Monash University. http://doi.org/10.1093/humrep/dead156

Annex

Annex 1 WP4 parameters-definitions 2023

Develop a list of core, standardized parameters with corresponding definitions on which data is to be collected

Part 1: Parameters to be included in the register

Centre code

Validation cell: suggestion= landcode + 4 digits, ex 32-0001
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**

Validation cell: provided for each individual involved in MAR, person who gets the treatment + partner (can be more than 1 during life)
Validation crosslink: if two codes (both partners) they need to be linked
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)

Validation cell: tick box
Validation crosslink: depending on what was chosen, certain modules/parts will become visible: a, b go to Module 2, then 3; c, d go to Module 2

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 cleavage stage 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]

Validation cell: drop-down list

Validation crosslink: /

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

Validation cell: yyyy/mm

Validation crosslink: date may not give an age of below 10y and over 60y

Definition:

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

5. Female Body Mass Index (BMI)

Validation cell: two digits (kg/m^2)

Validation crosslink: /

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)

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

6. Female current smoking status

a. Yes
b. No
c. Unknown

Validation cell: tick box
Validation crosslink:/
Definition:
A recorded variable based on several questions about cigarette smoking

7. Male Date of Birth (if male partner available)

Validation cell: yyyy/mm
Validation crosslink: /
Definition:
The day of birth for the male undergoing the ejaculated or surgically retrieved sperm collection.

8. Male Body Mass Index (BMI) (if male partner available)

Validation cell: : two digits (kg/m^2)
Validation crosslink: /
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 (if male partner available)

a. Yes
b. No
c. Unknown

Validation cell: tick box
Validation crosslink: /
Definition:
A recorded 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)

Validation cell: tick boxes, multiple options possible on the different levels
Validation crosslink: Depending on whether you tick Female/male/… different list of options appears
Combinations possible of all 4 options (eg female+male or male + genetic reason,…)

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 endometriotic 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)

Psychosexual (can be an indication for IUI and occasionally IVF): An anatomical abnormality or a functional disorder in an individual that precludes sexual intercourse

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

Validation cell: yes/no
Validation crosslink: /
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

Validation cell: yyyy/mm/dd
Validation crosslink: link between all dates in different modules
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 Progestogens
e. Combination

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

Other

Validation cell: tick boxes
Validation crosslink: Only to be completed if 11a

14. Cancellation prior to Ovum Pick Up (OPU)

a. Yes
b. No

Validation cell: yes/no
Validation crosslink: if yes go to 15, if no go to 16
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

Validation cell: tick box, different options possible
Validation crosslink: If 14 yes, end treatment
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

16. Date of OPU

Validation cell: yyyy/mm/dd
Validation crosslink: link between all dates in different modules. Not earlier than stimulation date or start of natural cycle and not later than transfer date
Definition: The date when ovum pick up (OPU) occurred.

17. Number of cumulus oocytes retrieved

Validation cell: maximum 2 digits
Validation crosslink: ≥ N of oocytes cryopreserved and/or ≥ N of oocytes inseminated or injected
Definition: The number of cumulus oocytes retrieved at OPU

18. In-vitro maturation (IVM)

a. Yes
b. No

Validation cell: yes/no
Validation crosslink: /
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

Validation cell: maximum 2 digits
Validation crosslink: ≤ N of cumulus oocytes retrieved (17)
If >0, then 20
If 19=17, then end treatment after 21
Definition:
The number of oocytes cryopreserved 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

Validation cell: tick box
Validation crosslink: if 19=17, then end treatment (only reason needed)
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

Validation cell: maximum 2 digits
Validation crosslink: ≤ N of oocytes inseminated or injected
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

Validation cell: tick box
Validation crosslink: /
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 oocyte collection)

b. Type of oocytes
   1. Fresh
   2. Frozen
   3. Combination of fresh and frozen

Validation cell: tick box
Validation crosslink: /
If "a2" is chosen: ask age donor of oocytes at time of collection,
Link with modules on donor material and frozen cycles
Definition: /

24. Date of insemination

Validation cell: yyyy/mm/dd
Validation crosslink: later than OPU, earlier than transfer
Definition: Date when sperm and oocyte are brought together

25. Insemination technique used:

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

Validation cell: tick box
Validation crosslink: If "a" then 26 and 28, if "b", then 27 and 29, if "c" then 26, 27, 28 and 29, if "d" go to module IUI

26. Number of oocytes inseminated (IVF)

Validation cell: maximum 2 digits
Validation crosslink: ≤ 17, ≥ 28 OR if "25c" then 26+27≤ 17 and ≥28+29
Definition: Number of oocytes in which a sperm cell has entered

27. Number of oocytes injected (ICSI)

Validation cell: 2 digits
Validation crosslink: : ≤ 17, ≥29 OR if "25c" then 26+27≤ 17 and ≥28+29
Definition: Number of oocytes in which a sperm cell was injected

28. Number of 2 pronuclei (2pn) – IVF

Validation cell: maximum 2 digits
Validation crosslink: ≤26, OR if "25c" then 26+27 ≥28+29,
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

Validation cell: maximum 2 digits
Validation crosslink: ≤27, OR if "25c" then 26+27 ≥28+29
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)

Validation cell: maximum 2 digits
Validation crosslink: ≤ 28+29

31. Number of embryos cryopreserved

Validation cell: maximum 2 digits
Validation crosslink: ≤ 30, =32+33
If =30, then end of treatment (only reason needed, fill in34)

32. Optional: Number of cleavage stage embryos cryopreserved

Validation cell: maximum 2 digits
Validation crosslink: = 31-33
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

Validation cell: maximum 2 digits
Validation crosslink: =31-32
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

Validation cell: tick box
Validation crosslink: if 30=31, then end treatment

35. Pre-implantation Genetic Testing

a. No
b. Yes

If yes,

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

Validation cell: multiple resp. if aneuploidy + monogenic disease are present simultaneously
Validation crosslink: only if 34b is indicated
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

Validation cell: yes/no
Validation crosslink: if yes, go to 37, if no go to 49
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

Validation cell: tick box
Validation crosslink: If fresh go to 38-41, if frozen go to 42-48, if combination go to 38-48

Use of fresh embryos

38. Date of embryo transfer

Validation cell: yyyy/mm/dd
Validation crosslink: If 36 =YES and 37 is "a" or "c" + link to date of OPU if available, later than date of insemination
If 37c, than 38=45
Definition:
Date on which the embryos are transferred to the uterus

39. Number of cleavage stage embryos transferred.

Validation cell: 1 digit
Validation crosslink: 39≤30

40. Number of blastocysts transferred.

Validation cell: 1 digit
Validation crosslink: 40≤30

41. Embryo Transfer Outcome

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

Validation cell: tick box
Validation crosslink: If a go to 50, if b or c, end treatment
If 37c, then 41=48

Use of frozen embryos

42. Date of thawing

Validation cell: yyyy/mm/dd

Validation crosslink: If 36=YES and 37="b" or "c" + link to date of insemination

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, aromatase inhibitors, SERMs)

Validation cell: tick box

Validation crosslink: /

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

Validation cell: yes/no

Validation crosslink: /

Definition:

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

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

Validation cell: yyyy/mm/dd

Validation crosslink: If 36=YES and 37="b" or "c" + link to date of OPU (fresh cycle), later than date of fertilization

If 37c, than 38=45

46. Number of cleavage stage embryos transferred.

Validation cell: maximum 1 digit

Validation crosslink: if "32" available then 46≤32, if only linked to 1 OPU, otherwise different OPU should be linked by date

47. Number of blastocysts transferred.

Validation cell: maximum 1 digit
Validation crosslink: if "33" available then 47≤33 if only linked to 1 OPU, otherwise different OPU should be linked by date

48. Embryo Transfer Outcome

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

Validation cell: tick box
Validation crosslink: If "a" go to 50, If "b" or "c" end of treatment
If 37c, than 41=48

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

Validation cell:
Validation crosslink: only if 36 =NO
Definition:

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

Validation cell: tick box
Validation crosslink: to be completed if 41a or 48a
If Yes go to 51
If No go to 52
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

Validation cell: tick box, multiple options possible
Validation crosslink: only if 50 = yes
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

Validation cell: 1 digit

Validation crosslink: If "0", then end only biochemical pregnancy and stop treatment cycle; If "1" then go to 55, if "2 or more", then go to 53

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

Validation cell: tick box

Validation crosslink: to be completed if 52≥2

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

Validation cell: tick box

Validation crosslink: Only if "52" is 1 or more

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

Validation cell: tick box
Validation crosslink:/
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

Validation cell: yyyy/mm/dd
Validation crosslink: To be completed if "55f "; cannot be before 20 weeks of OPU or FET date and not later than 41 after OPU or FET date (calculates gestational age)
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

Validation cell: 1 digit
Validation crosslink: depending on this number, options for liveborn children
Definition:/

58. Number of stillbirths

Validation cell: 1 digit
Validation crosslink: /

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

Validation cell: tick box
Validation crosslink: **/**
Definition:/

60. Birth weight

Validation cell: grammes
Validation crosslink: /
Definition:
Weight of the newborn at birth

61. Neonatal outcome

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

Validation cell: tick box
Validation crosslink: /
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

Validation cell: tick box
Yes, only if relevant medical records are available. If not, answer should be "unknown"
Validation crosslink: /
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

To be completed if 2e or 2f
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 no: outcome
- HCG detected (Positive Pregnancy test)
- No HCG detected (Negative pregnancy test)
- Lost to follow-up

Validation cell: tick box
Validation crosslink: If HCG detected go to 50, If no HCG or Lost to follow up: end of treatment

Link to complications and pregnancy

Module 9 – Fertility preservation

To be completed if 2g

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

Validation cell: tick box
Validation crosslink:/
Definition:

64. Reason for fertility preservation

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

Validation cell: tick box
Validation crosslink:
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

# 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.