Protocol full title Randomized Controlled Trial:

Gynecologists' feedback on **A**RT-**P**regnancy rates: a **r**andomized **c**ontrolled **t**rial (s62972)

Acronym:

GAP-RCT

Version and date of final protocol:

Version 3, September 30th, 2019

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0. Study synopsis

Study title	**G**ynecologists' feedback on **A**RT-**P**regnancy rates: a **R**andomized **C**ontrolled **T**rial
Short title	GAP-RCT
Sponsor name	KU Leuven
Principal Investigator	Professor Dr. Karen Peeraer (UZ Leuven)
Medical condition/ disease under investigation	Infertility treated with IVF
Study purpose	We will examine the hypothesis that women who are given their personalized IVF-prognosis are less likely to overestimate their IVF-live birth rate, as compared to women who do not receive a personalized IVF-prognosis. Control group: At the time of their fresh embryo transfer couples will receive a document with a photo of their transferred embryo(s) and the number of cryopreserved embryos. Intervention group**:** At the time of their fresh embryo transfer couples will receive a document with the following feedback: a photo of their transferred embryo, the number of cryopreserved embryos, the quality rating of the transferred embryo's (i.e. ★, ★★, ★★★, ★★★★), and couple's **personalized IVF-prognosis** (i.e. their chance on a live birth from the current IVF-cycle, including the transfer of fresh and if available cryopreserved embryos, calculated by entering eight background characteristics and five IVF-laboratory results into a prognostic model).
Primary outcome	The **proportion of women expecting their IVF-live birth rate to be double their calculated IVF-prognosis**, directly after their fresh embryo transfer.
Secondary outcomes	The **proportion of men expecting** their IVF-live birth rate to be double their calculated IVF-prognosis, directly after their fresh embryo transfer. **Women's and men's anxiety** will be assessed with the reliable 'State-Anxiety Inventory, (STAI-state)' questionnaire, disseminated in coded paper-pencil format on the day of the fresh embryo transfer. **Patient's infertility-specific distress** will be assessed with the reliable 'Infertility Distress Scale (IDS)' questionnaire, disseminated via text message and online within two days of the conclusive pregnancy test after the transfer of the last (fresh or cryopreserved) embryo of the studied IVF-cycle.
Background variables	The following variables that potentially affect patient's expected live birth rate will be extracted from patient's medical file: whether they already had an ART-child (i.e. yes/no) and how many unsuccessful embryo transfers they had in the past (i.e. number). In addition, both partner's general optimism, will be assessed with the reliable questionnaire 'LOT-R' which will be disseminated in coded paper-pencil format on the day of oocyte aspiration.
Feasibility outcome	On the day of their fresh embryo transfer, men and women will be asked to fill out two questions on uptake and evaluation of the standardized personalized feedback.

Follow-up outcomes	Long-term clinical and compliance outcomes will be followed-up in couple's medical chart 12-18 months after the oocyte aspiration. More specifically, the 12-months cumulative clinical live birth rates for the observed oocyte aspiration will be extracted from the medical chart. In addition, the following compliance outcomes will be extracted: (i) censored by their medical doctor to discontinue IVF (yes-no) , (ii) number of untreated cycles within 12-months after oocyte aspiration and prior to the start of a new fresh cycle while not pregnant (i.e. IVF-delay), (iii) whether or not a subsequent IVF-cycle was started within twelve months after the last failed pregnancy test while not pregnant and no medical censoring to discontinue (i.e. IVF-discontinuation).
Study design	RCT (computerized randomization; 1/1 allocation sequence; no blinding)
Endpoints	The expected IVF live birth rate, anxiety and infertility specific distress of women and men.
Sample size	Hypothesizing that the intervention can lower the proportion of women expecting their live birth rate to be double their calculated IVF-prognosis from 50% to 25% dictates a sample size of 64 women per group (two-sided test; power 80%; α=0.05; G*Power). To account for a 15% chance of study drop-out due to not filling-out the questionnaires or loss of follow-up, **74 ~~80~~ women will be recruited per group.**
Summary of eligibility criteria	Inclusion criteria: Couples treated with a **2nd-6th fresh cycle of IVF** (i.e. IVF with or without ICSI; every couple can only participate ones in this study). Exclusion criteria, Couples treated with: • Pre-implantation Genetic Diagnosis (PGD) • donated oocytes, sperm or embryos • Spermatozoa obtained by testicular extraction (ICSI-CRYO-TESE) • HIV-positive diagnosis • Embryo transfer on day 2
Maximum duration of study participation for a subject	Study participation will be during one IVF-cycle. Men and women of eligible couples will be asked to each fill out a questionnaire on the day of oocyte aspiration, on the day of fresh embryo transfer and within two days of the pregnancy test after the transfer of the last embryo. Filling out each questionnaire takes 5 minutes.
Version and date of final protocol	Version 3, September 30, 2019
Version and date of protocol amendments	Not applicable

1. Background and rationale

The general population is known to overestimate *in vitro* fertilisation (IVF) success rates[1,2]. Qualitative interviews showed that well informed women cryopreserving their oocytes were unrealistically optimistic about their own chances of having a child as they thought they and/or their gynaecologist were better than average[3]. To the best of our knowledge, the live birth rates expected by infertile couples during their IVF-cycle (i.e. in real life treatment situations) has yet to be studied. In addition, whether these expected live birth rates are affected by factors like gender, previous treatment experiences and level of optimism is unknown.

IVF-success rates expected by patients are especially relevant since patients shared in interviews that the combination of unrealistically high expected live birth rates and repeated unsuccessful IVF-cycles, caused distress, which ultimately led to discontinuation from IVF[4]. The association between patient's expected IVF-success rates and their level of distress experienced at the time of a negative pregnancy test and decision to discontinue IVF has yet to be quantified prospectively.

Fertility patients have indicated that they want personalized information, for example on which success rate to expect[5-7]. Recently, prognostic models that calculate personalized and cycle-specific success rates, have been developed and validated[8,9]. So far, no study has examined whether gynaecologist's feedback to couples about their personalized IVF-prognosis influences patient's expected IVF-success rate.

Based on retrospective analysis of data from couples treated with a 2nd - 6th IVF-cycle by our laboratory, our group developed a model to give couples a personalized IVF-prognosis on the day of their embryo transfer based on eight background characteristics and five IVF-laboratory results from their current IVF-cycle. Our prognostic model performs exceptionally well as compared to previously published models. More specifically, our model has a c-statistic of 0.74 and the c-statistic of previously published IVF-models ranges between 0.50 and 0.73[9-15]

2. Study objectives and design

2.1 Study objective

We will examine the hypothesis that women who are given their personalized IVF-prognosis are less likely to overestimate their IVF-live birth rate, as compared to women who do not receive a personalized IVF-prognosis.

2.2 Study design

At the time of oocyte aspiration, patients will be randomised in two groups:

- Control group: At the time of their fresh embryo transfer couples will receive a document with a photo of their transferred embryo(s) and the number of cryopreserved embryos.
- Intervention group: At the time of their fresh embryo transfer couples will receive a document with the following feedback (Appendix 5): a photo of their transferred embryo, the number of cryopreserved embryos, the quality rating of the transferred embryo's (i.e. ★, ★★, ★★★, ★★★★, appendix 6), and couple's personalized IVF-prognosis (i.e. their chance on a live birth from the current IVF-cycle, including the transfer of fresh and if available cryopreserved embryos), calculated by entering eight background characteristics and five IVF-laboratory results into a prognostic model[8,9] (Appendix 7).

Firstly, we wish to analyse whether personalized information on IVF-prognosis on the day of their fresh embryo transfer results in more realistic expected IVF-live birth rates.

Secondly, we wish to evaluate whether sharing these IVF-prognosis with patients at the time of embryo transfer is associated with the anxiety experienced by patients.

Thirdly, we wish to explore whether these IVF-live birth rates expected by patients are associated with the infertility specific distress experienced by patients at the time of a negative pregnancy test.

Fourthly, we wish to follow-up whether these IVF-live birth rates expected by patients are associated with clinical and compliance outcomes.

2.3 Study parameters/endpoints

The **primary endpoint** is the **proportion of women expecting** directly after their fresh embryo transfer that **their IVF-live delivery birth rate to be double their calculated IVF-prognosis** (i.e. women's expected live birth rate ≥ 2*prognose) In addition **the proportion of men expecting their IVF-live birth rate to be double their calculated IVF-prognosis** will be studied. Patient's expected IVF-live birth rates will be assessed immediately after the fresh embryo transfer with a single question coded paper-pencil questionnaire.

Women's and men's anxiety will be assessed with the reliable 'State-Anxiety Inventory, (STAI-state)' questionnaire[16 17] disseminated in coded paper-pencil format on the day of the fresh embryo transfer (Appendix 3). The STAI-state questionnaire includes 20 questions rated on a-four-point-Likert scale and results in a score between 20 to 80 (the higher, the more anxiety).

Patient's infertility-specific distress will be assessed with the reliable 'Infertility Distress Scale (IDS)' questionnaire [18], which has been translated reciprocally to Dutch (Appendix 4). The IDS questionnaire will be disseminated via text message and online within two days of the conclusive pregnancy test after the transfers of the last (fresh or cryopreserved) embryo of the studied IVF-cycle. The IDS questionnaire includes eight questions to be rated on a-five-point-Likert scale and results in a score between 8 and 40 (the higher, the more infertility specific distress, Appendix 4).

2.4 Follow-up parameters/endpoints

Long-term clinical and compliance outcomes will be followed-up in couple's medical chart twelve-eighteen months after the oocyte aspiration. More specifically, the 12-months cumulative clinical live birth rates for the observed oocyte aspiration will be extracted from the medical chart. In addition, the following compliance outcomes will be extracted: (i) censored by their medical doctor to discontinue IVF, (ii) number of untreated cycles within 12-months after oocyte aspiration and prior to the start of a new fresh cycle while not pregnant (i.e. IVF-delay), (iii) whether or not a subsequent IVF-cycle was started within twelve months after the last failed pregnancy test while not pregnant and no medical censoring to discontinue (i.e. IVF-discontinuation;[19,20])

2.5 Study design

RCT (computerized randomization; 1/1 allocation sequence; no blinding)

3. Methodology

3.1 Study population and sample size

3.1.1 Study population

Inclusion criteria:

All couples treated at the Sint Augustinus Fertility clinic (Wilrijk) with a 2nd-6th fresh cycle of IVF are eligible. IVF includes IVF with or without ICSI and every couple can only participate ones in this study. Couples treated with their first IVF-cycle are not eligible, since they are not the priority target population for this study. According to qualitative research discontinuation from IVF can amongst others be explained by the combination of high expectations regarding IVF-live birth rates and having experienced several cycles of unsuccessful IVF.

Exclusion criteria:

- Couples going through IVF because they have an indication for **Pre-implantation Genetic Diagnosis (PGD)** are excluded as this study explores possible associations between IVF live birth rates expected by patients and infertility specific distress. The latter is less relevant to PGD-couples who turn to IVF for a genetic indication and not because of fertility problems.
- Couples treated with **donated** oocytes, sperm or embryos
- Couples treated with spermatozoa obtained by testicular extraction **(ICSI-CRYO-TESE)**
- **HIV-positive** patients

3.1.2 Sample size calculation

Hypothesizing that the intervention can lower the proportion of women expecting their live birth rate to be double their calculated IVF-prognosis from 50% to 25% dictates a sample size of 64 women per group (two-sided test; power 80%; α=0.05; G*Power). To account for a 25% chance of study drop-out due to no embryos for transfer, not filling-out the questionnaires or loss of follow-up, 80 women will be recruited per group.

3.2 Study procedures including recruitment and data-collection

The main outcomes of this study are gathered on the days of OPU and Embryo transfer as presented in figure 1.

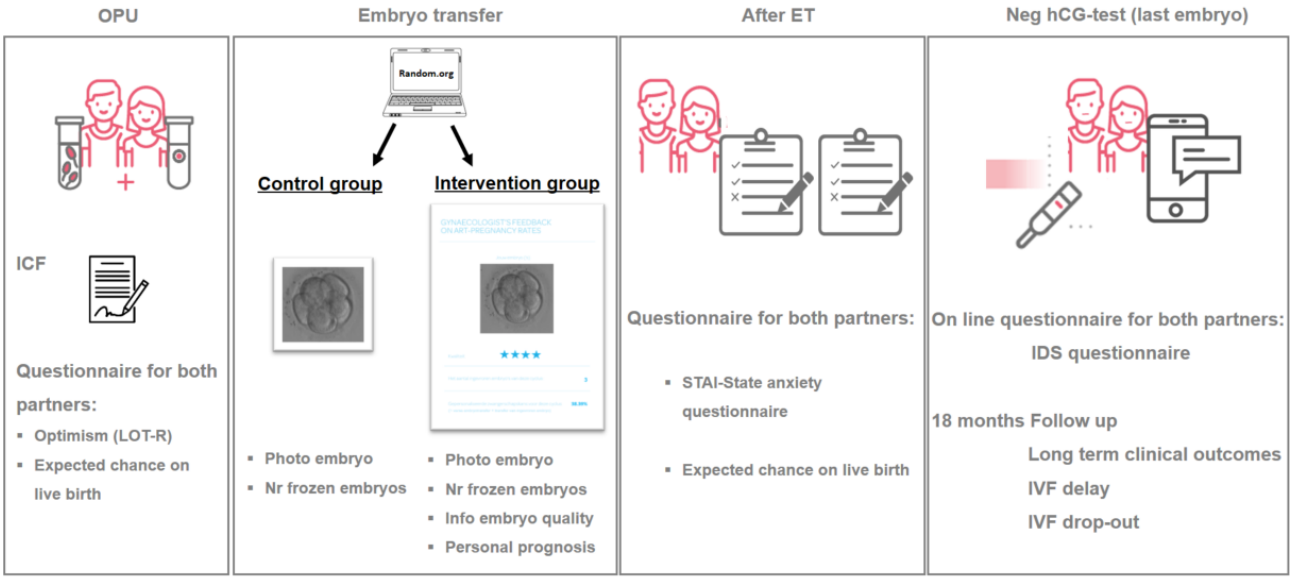

Figure 1: Study procedure and data collection for participating couples of the GAP-RCT

On the day of their oocyte aspiration, couples will be informed on the study and asked for their informed consent. Consenting men and women of eligible couples will be asked to each fill out a questionnaire on expected live birth rate (Appendix 1) and the LOT-R questionnaire (Appendix 2) on general optimism.

On the day of their fresh embryo transfer, couples are randomized. Couples in the control group receive a document with a photo of their embryo(s) and the number of cryopreserved embryos. Couples in the intervention group receive a document with a photo of their transferred embryo(s), its quality rating, the number of cryopreserved embryos and couple's personalized IVF-prognosis (Appendix 5). Men and women of both groups will be asked to fill out the questionnaire on expected live birthrate (Appendix 1) and the STAI-state questionnaire on anxiety (Appendix 3).

Within two days of the conclusive pregnancy test after the transfers of the last (fresh or cryopreserved) embryo of the studied IVF-cycle, the IDS questionnaire on Patient's infertility-specific distress [18] will be disseminated via text message and online (appendix 4).

Eighteen months after the embryo transfer of the last (fresh or cryopreserved) embryo of the studied IVF-cycle, the researchers will follow-up the long-term clinical and compliance outcomes in patient's medical chart (i.e. censored by their medical doctor to discontinue IVF, IVF-delay and IVF-discontinuation).

3.3 Withdrawal of individual subjects

Subjects can stop their participation in study at any time without having to give a reason. If this happens, only the data collected until that point will be used.

4. Data-analysis

4.1 Overall statistical considerations

The collected data will be imported into the 'Statistical Package for the Social Sciences (SPSS)'.

The previously proven reliability of the scales of the LOT-R, the STAI-state and the IDS will be re-evaluated by calculating Cronbach's alpha statistics and Item Total Correlations.

The collected data will be described with absolute values or percentages for categorical variables and with measures of dispersion (e.g. mean and standard deviation) for continuous variables, which is in line with the standard method of analysis of the used standardized LOT-R, STAI-state and IDS questionnaires.

The gathered data will be described separately for men and women. We will, however, explore whether partners differ in expected live birth rates, general optimism and infertility specific distress with paired t-tests. In addition, whether partner's influence each other regarding these three outcomes and whether this is affected by gender will be explored with linear mixed models.

A p-value ≤0.05 will be considered statistically significant.

4.2 IVF-live birth rates expected by patients

The IVF-live birth rates expected by patients will be analysed for both groups and for men and women separately. We will conduct an intention to treat analysis, primarily focussing on whether the intervention and the control group differ in the likeliness that women expect a live birth rate, which is at least twice as big as their prognosis. The difference in this binominal outcome will be analysed with a Chi^2-test. A p-value ≤0.05 will be considered statistically significant. To also inform readers about the extent of the potential difference, proportions of the primary outcome will be reported per group and the 95% confidence interval of the difference in proportions of the primary outcome between both groups (i.e. if significant, it will not include 0) will also be reported[21,22].

4.3 Quantification of the under/over estimation of the live birth rates expected by patients

In addition to the primary outcome (i.e. evaluating the proportion of women expecting their IVF-live birth rate to be double their calculated IVF-prognosis directly after their fresh embryo transfer) we want to quantify this under/over estimation. This will be calculated using the following formula: (expected LBR-prognosis)/prognosis. A positive sign shows overestimation, a negative sign shows underestimation and the absolute value quantifies the extend of the over/underestimation. For both groups, the mean and SD will be calculated. In addition, the mean difference in misjudgement between both groups and it's 95% confidence interval (i.e. to give an impression of the preciseness of this estimation) will be reported[21].

4.4 Anxiety experienced by patients

Whether the intervention and control group, differ in anxiety on the day of their embryo transfer will be analysed by comparing both groups STAI-state with an independent sample t-test. A p-value ≤0.05 will be considered statistically significant and the mean difference in anxiety between both groups and it's 95% confidence interval will be reported[21].

4.5 Association between patient's general optimism and their expected live birth rates

Furthermore, we will assess in the entire sample with linear mixed models including 'couple number' as a random factor to take account of clustering within couples, if patient's general level of optimism is associated to their expected live birth rate.

4.6 Association between IVF-live birth rates expected by patients and infertility specific distress

Whether the intervention and control group, differ in infertility specific distress on the day of their embryo transfer will be analysed by comparing both group's IDS-score with an independent sample t-test. A p-value ≤0.05 will be considered statistically significant and the mean difference in infertility specific distress between both groups and it's 95%

confidence interval will be reported[21]. In addition, a linear (mixed or non-mixed) model will explore in the entire sample whether IVF-live birth rates expected by patients are associated with their infertility specific distress. We will examine whether gender significantly ($p \leq 0.05$) affects the association between the IVF-live birth rate expected by patients and their infertility specific distress. If it does, we will rely on linear (non-mixed) models per gender. If it does not, we will rely on linear mixed models while including 'couple number' as a random factor to take account of clustering within couples, as partners cannot be considered independent cases [23,24].

4.7 Follow-up outcomes

Whether the intervention and control group, differ in one long-term clinical (i.e. the 12-months cumulative clinical live birth rates for the observed oocyte aspiration) and three compliance outcomes, followed-up in patient's medical chart, will be analysed. The association between expected live birth rates and these long-term outcomes will also be explored on data from the entire sample.

5. Direct access to source data and documents

For this RCT no study-related monitoring or audits are planned. The EC review, and regulatory inspections (where appropriate) shall provide direct access to source data and other documents (i.e. patients' case sheets, etc.).

6. Safety reporting

6.1 Definitions

6.1.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

6.1.2 Adverse Reactions (ARs)

An AR is a response to a medicinal product or experiment which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product or study-related intervention and an AE is at least a reasonable possibility. ARs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include Special Situations.
For reporting purposes to Funder of this study, only AR related to a medicinal product of Funder must be documented by the site staff. An AR related to the intervention on the study must also be documented by the site staff, but not reported to the Funder.

6.1.3 Serious Adverse Reactions (SARs)

A SAR is any AR as defined above, which also fulfils at least one of the seriousness criteria below:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- that required medical or surgical intervention to preclude of any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate medical judgement. An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SARs to the sponsor without undue delay after obtaining knowledge of the events.

6.1.4 Special Situations with regards to a medicinal product of Funder

- Use of such medicinal product during pregnancy or breastfeeding: reports where embryo, fetus or child may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure);
- Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure;

- Lack of therapeutic efficacy;
- Prescription error/dispensing error, e.g., due to confusion of invented names of the medicinal products;
- Drug interaction;
- Suspected transmission of an infectious agent via a medicinal product; or
- Product complaints (incl. falsified products or counterfeit products).

The investigator will report all above listed situations to the sponsor without undue delay after obtaining knowledge of the events.

6.1.5 Emerging Safety Issues

Safety issues are events/observations which may occur in relation to a medicinal product of Funder and which may have major impacts on the risk-benefit balance of the product and/or patients or public health.

6.2 Recording of adverse events

Safety events will be recorded from informed consent signature until the day of their last embryo transfer. This study does not affect couple's treatment and we do not expect physical risks from giving patients their personalized prognosis. The personalized prognosis might, however, increase anxiety on the day of embryo transfer and this will be monitored with a validated questionnaire during the study. In addition, participant's reports of distress, potentially made to medical doctors during embryo transfer or reported on the questionnaire administered directly after the transfer will be registered.

The participant will be asked to report any adverse event related to the study-specific intervention to the study team. These reported events will be documented by the Investigator in the source documents. The following minimum information should be recorded for each AR:

- AE description of the adverse events
- Start and stop date of the AR
- Severity
- Seriousness
- Causality assessment to the study interventions
- Outcome

6.3 Reporting to the Ethics Committee

The sponsor will assess whether any relevant safety information that becomes available during the study should be reported ad hoc to the EC.

The sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

7. Ethics and regulatory approvals

7.1 Regulation statement

The study will be conducted in compliance with the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

The study protocol and all other study-related information shall be submitted to the Ethics Committees of the Participating Sites and the national competent authorities where applicable, in order to obtain prior approval before the study is initiated, unless such submission to the Ethics Committee is not required by applicable national legislation or in the event of a waiver for submission has been granted. Any subsequent protocol amendments will be submitted to the appropriate Ethics Committees and national Regulatory Authorities for approval.

Unless not required by applicable national legislation, the study will be conducted only on the basis of prior informed consent by the study subjects, or their legal representatives, to participate in the study. The Participating Site shall

obtain a signed informed consent form (ICF) for all patients prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the (local) Ethics Committee, if required. The Participating Site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

The Investigator and the Participating Site shall treat all information and data relating to the study disclosed to Participating Site and/or Investigator in this study as confidential and with respect for the study participant's privacy and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the study. The collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with applicable personal data protection and the processing of personal data (EU Directive 95/46/EC and its transposing national legislation).

The data shall be coded, which means that there continues to be a link between the data and the individual who provided it. The research team is obligated to protect the data from disclosure outside the research team according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers should be stored separately from their research data and replaced with a unique code to create a new identity for the subject. Note that coded data are not anonymous.

7.2 Recruitment and consent

Couples will be asked for informed consent on the day of their oocyte aspiration. Patients who agree to participate will be asked to sign a written informed consent of which they will receive a copy.

7.3 Compensation for injury

The sponsor has obtained dispensation from the statutory obligation to provide insurance. Due to the nature of the study, there are no additional risks.

8. Publication policy

The parties agree that publications or presentations of any of the results from the study shall be in accordance with accepted scientific practice, academic standards and customs. It is anticipated that the results of the overall study shall be published in an international peer reviewed journal. Publications will be coordinated by Dr. Dancet. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

9. Insurance/indemnity

Sponsor shall be liable, even without fault, for any damages incurred by a study patient and linked directly or indirectly to the participation to the study. Sponsor shall enter into an insurance agreement in order to cover the liability for any damages incurred by the Belgian study participants.

10. Funding

Not applicable.

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12. Appendices

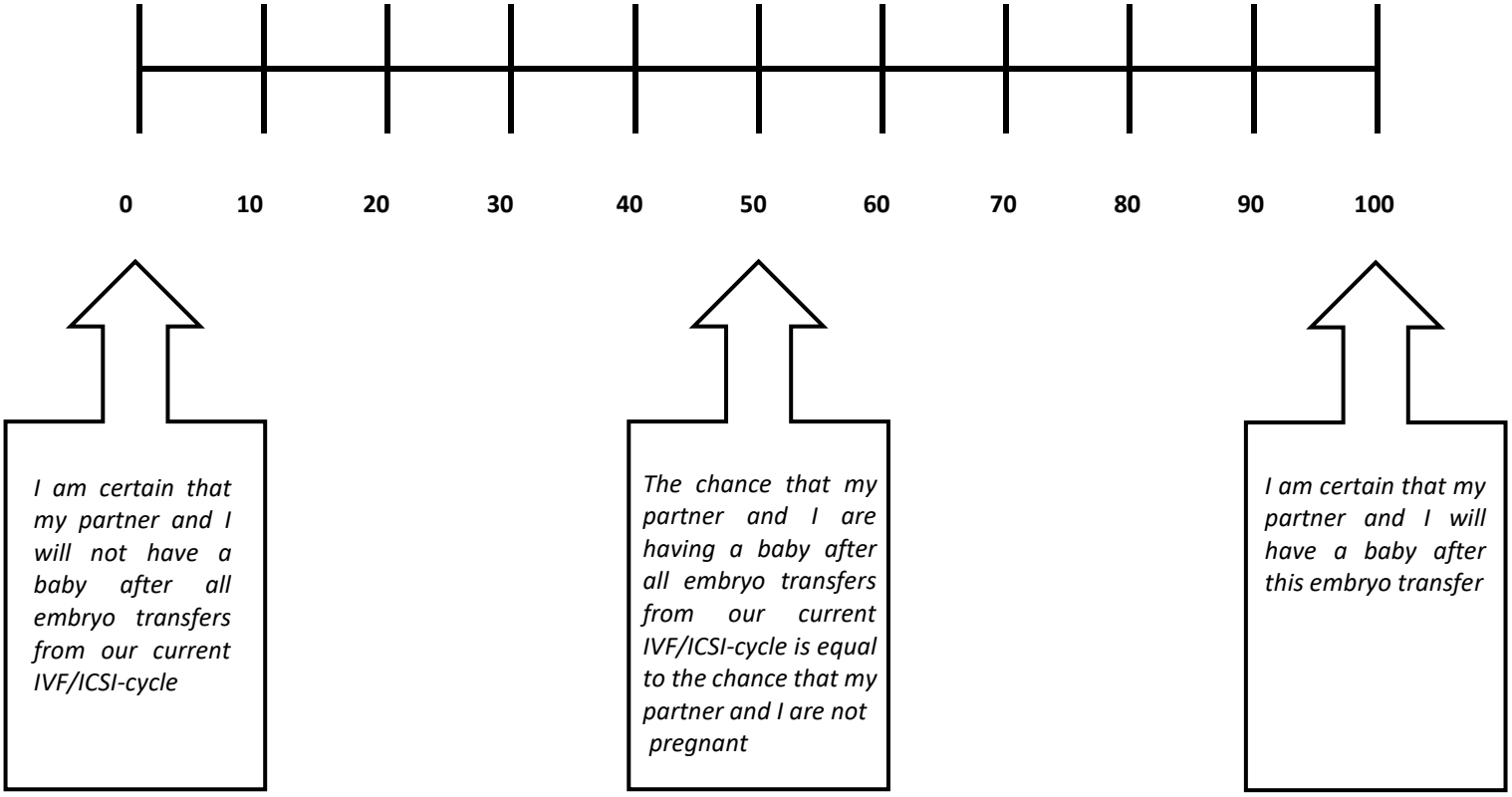
Appendix 1: Questionnaire on IVF-live birth rates expected by patients

Your gynaecologist told you which success rates he/she expects in your case but we are interested in your expected IVF-live birth rate.

What, do you think, is the chance that you or your partner will deliver after all the embryo transfers of your current IVF/ICSI-cycle?

This includes both the current fresh embryo transfer and, in case embryos have been frozen, subsequent frozen embryo transfers.

(Please indicate your response with a 'X' on the bar below, the arrows below explain the meaning of some possible answers)



Appendix 2: LOT-R questionnaire on general optimism (Scheier et al, 1994)

Please be as honest and accurate as you can throughout. Try not to let your response to one statement influence your responses to other statements. There are no "correct" or "incorrect" answers. Answer according to your own feelings, rather than how you think "most people" would answer.

In uncertain times, I usually expect the best.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

It's easy for me to relax.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

If something can go wrong for me, it will.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

I'm always optimistic about my future.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

I enjoy my friends a lot.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

It's important for me to keep busy.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

I hardly ever expect things to go my way.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

I don't get upset too easily.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

I rarely count on good things happening to me.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

Overall, I expect more good things to happen to me than bad.
- I agree a lot
- I agree a little
- I neither agree nor disagree
- I disagree a little
- I disagree a lot

Appendix 3: the STAI-state questionnaire on state anxiety

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you feel right now, that is, at this moment. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	Not at all	Somewhat	Moderately so	Very much so
I feel calm	☐	☐	☐	☐
I feel secure	☐	☐	☐	☐
I am tense	☐	☐	☐	☐
I feel strained	☐	☐	☐	☐
I feel at ease	☐	☐	☐	☐
I feel upset	☐	☐	☐	☐
am presently worrying over possible misfortunes	☐	☐	☐	☐
I feel satisfied	☐	☐	☐	☐
I feel frightened	☐	☐	☐	☐
I feel comfortable	☐	☐	☐	☐
I feel self-confident	☐	☐	☐	☐
I feel nervous	☐	☐	☐	☐
I am jittery	☐	☐	☐	☐
I feel indecisive	☐	☐	☐	☐
I am relaxed	☐	☐	☐	☐
I feel content	☐	☐	☐	☐
I am worried	☐	☐	☐	☐
I feel confused	☐	☐	☐	☐
I feel steady	☐	☐	☐	☐
I feel pleasant	☐	☐	☐	☐

Appendix 4: IDS questionnaire on infertility specific distress (Pook&Krause, 2005)

This questionnaire deals with your distress due to your (couple) infertility. Please indicate what applies best to you at this moment in time.

		Not at all	A little	Somewhat	A lot	Very much
1	To which extend are you distressed due to the last menstruation (and therefore no pregnancy)?	☐	☐	☐	☐	☐
2	To which extend are you distressed due to your infertility as a whole?	☐	☐	☐	☐	☐
3	To which extend is having a child important to you?	☐	☐	☐	☐	☐
4	To which extend do you appraise your infertility as a challenge?	☐	☐	☐	☐	☐
5	To which extend do you appraise your infertility as a threat?	☐	☐	☐	☐	☐
6	To which extend do you feel helpless due to your infertility?	☐	☐	☐	☐	☐
7	How often do you think of your infertility?	☐	☐	☐	☐	☐
8	How big is your desire to have a child?	☐	☐	☐	☐	☐

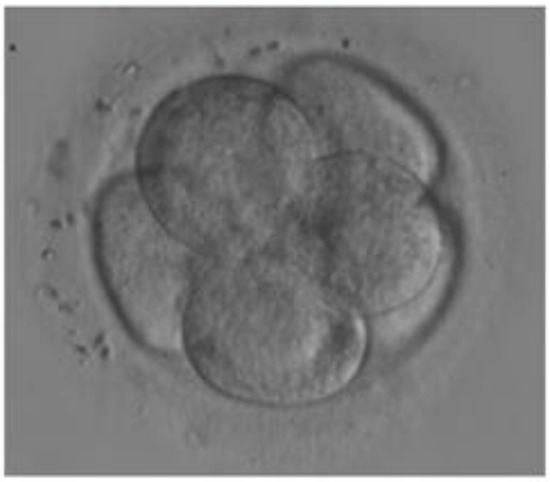
Appendix 5: Document with personalized information given at the time of embryo transfer to patients in the intervention group

NAAM PATIENT 811111V111
NAAM PARTNER 811111M111
GAP-CS-XX

UZ LEUVEN

GYNAECOLOGIST'S FEEDBACK ON ART-PREGNANCY RATES

Jouw embryo ('s)



Kwaliteit ★★★★

Het aantal ingevroren embryo's van deze cyclus: 3

Gepersonaliseerde zwangerschapskans voor deze cyclus **38.39%**
(= verse embryotransfer + transfer van ingevroren embryo)

Appendix 6: LUFC embryo quality rating

LUFC-embryo rating based on embryo scoring at day three* or day five				
	Reduced quality	**Reasonable quality**	**Good quality**	**Top quality**
	★	★★	★★★	★★★★
Day three	<6 cells >3 fragmentation	600 - 601 - 610 - 611 - 620 - 621 602 - 612 - 622 722 - 822 - 922 - 1022	720 - 721 - 702 - 712 820 - 821 - 802 - 812 920 - 921 - 902 - 912 1000 - 1001 - 1010 - 1011 1020 1021 - 1002 - 1012	700 - 701 - 710 – 711 800 - 801 - 810 – 811 900 - 901 - 910 – 911 M
Day five	Morula or less	Very early blastocyst Early blastocyst Expanding blastocyst	Expanded blastocyst Hatching blastocyst Hatched blastocyst	

*The LUFC day three embryo scoring includes three digits:

- The first number indicates number of cells.
- The second number indicates degree of fragmentation (i.e. 0= no; 1< 10 %; 2= 10-25%; 3= 25-50%; 4>50%).
- The third number indicates symmetry of cells: (0= symmetric; 1= minor asymmetry; 2= asymmetric as ≥ 50% difference in size between cells)

Appendix 7: The thirteen factors which will be taken into account by the prognostic model [8,9]

The prognostic model takes account of the following thirteen factors:

- Female age
- duration of infertility
- previous ongoing live birth
- male subfertility
- diminished ovarian reserve
- endometriosis
- basal FSH
- number of failed IVF cycles
- fertilization in the previous IVF-cycle
- number of embryos in the current IVF-cycle
- mean morphological score per day 3 embryo in the current IVF-cycle
- presence of 8-cell embryos on day 3 in the current IVF-cycle
- presence of morulae on day 3 in the current IVF-cycle

The relative weight of the variables included in the Adapted van Loendersloot model					
Variables		Background coding binary variabels	Adapted model		
			Beta	Standard Error	P
Intercept			1.796	16.225	0.912
Couple characteristics	Age	-	0.023	1.499	0.988
	Age x age	-	0.000	0.046	0.998
	Age x age x age	-	0.000	0.000	0.947
	Duration of infertility (years)	-	-0.121	0.060	0.044
	Previous live birth (yes/no)	Yes=0; No=1	-0.061	0.167	0.715
	Male infertility (yes/no)	Yes=0; No=1	0.799	1.164	0.492
	Diminished ovarian reserve (yes/no)	Yes=0; No=1	0.250	0.312	0.423
	Endometriosis (yes/no)	Yes=0; No=1	0.265	0.190	0.163
	Basal FSH (IU/mL)	-	-0.130	0.082	0.114
	Number of previous failed IVF-cycles	-	-0.088	0.070	0.205
	Age x male infertility	-	0.028	0.034	0.409
	Endometriosis x Diminished ovarian reserve	Yes=0; No=1	-0.166	0.544	0.760
	Embryo after ovum retrieval in the previous cycle (yes/no)	Yes=0; No=1	0.150	0.257	0.559
Current cycle characteristics	Number of embryos after ovum retrieval	-	0.153	0.029	0.000
	Mean morphological score all embryos day three	-	-0.581	0.100	0.000
	Eight cell embryo on day three (yes/no)	Yes=0; No=1	-0.199	0.185	0.281
	Morulae on day three (yes/no)	Yes=0; No=1	-0.697	0.456	0.126

De formule waarmee de prognose wordt berekend:

Probability = $e^y/(1+e^y)$

Met

y = 1.796 + (0.023*Age) + (-0.121*Duration of infertility) + … + (-0.697*Morulae present on d3)

Appendix 8: Self-developed questionnaire on uptake and assessment of on-paper personalized feedback

Please share your uptake and assessment of the 'on-paper personalized feedback' which included a photo of your embryo, the quality of your embryo and your personal and cycle-specific chance of a live birth.

	0	1	2	3 or more
How did you look at your on-paper personalized feedback?	☐	☐	☐	☐

	Definitely not	Probably not	Probably	Definitely
Would you advise your friends or family who go through IVF at the same clinic to ask for the on-paper personalized feedback?	☐	☐	☐	☐

DATA PROCESSING ANNEX ("DPA") TO THE PROTOCOL

Definitions:

"**Protocol**" means the document entitled "Gynaecologists' feedback on ART-Pregnancy rates: a randomized controlled trial" (GAP-RCT) containing the details of the academic study as developed by the Sponsor as approved by the relevant ethics committee.

"**Sponsor**" means Universitaire Ziekenhuizen Leuven

Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("**Data Processor**") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("**Data Controller**").

"**Applicable Law**" means any applicable data protection or privacy laws, including:

(i) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");

(ii) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;

"**Personal Data**" means any information relating to an identified or identifiable natural person ('**Data Subject**'), including without limitation pseudonimized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1) The Data Processor is instructed to process the Personal Data for the term of the Protocol and only for the purposes of providing the data processing tasks set out in the Protocol.
2) The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
3) The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
   (i) accidentally or unlawfully destroyed, lost or altered,
   (ii) disclosed or made available without authorization, or
   (iii) otherwise processed in violation of Applicable Law.
4) The appropriate technical and organizational security measures must be determined with due regard for:
   (i) the current state of the art,
   (ii) the cost of their implementation, and
   (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.
5) The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.
6) Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, in fulfilling its obligation to respond to requests from data subjects pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object).
7) The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with Data Processor, the findings as described under 9) (ii) below to the Data Controller.
8) The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.

9) The Data Processor must without undue delay in writing notify the Data Controller about:
   (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
   (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
   (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the data subjects or from third parties.
10) Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 9) (ii)(a) above will contain at least the following information:
   (i) The nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Subjects concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
   (ii) The likely consequences of the Personal Data breach;
   (iii) A proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
11) The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
12) The Data Processor must promptly reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 9) (ii) above and (b) any requests from Data Subjects under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.
13) The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 9) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

14) The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.
15) Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
16) The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data

Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.

For acknowledgment by Principal Investigator of GZA
Prof. dr. Peter De Loecker

5/9/2019
Date

Signed on behalf of Sponsor/Data Controller (Universitaire Ziekenhuizen Leuven)
Prof. Dr. Wim Robberecht

_____ _____
Date

Signed on behalf of Participating site / Data Processor
Johanna Devroe

5/9/2019
Date