

DE NOVO CLASSIFICATION REQUEST FOR NATURAL CYCLES

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Software application for contraception. A software application for contraception is a device that provides user-specific fertility information for preventing a pregnancy. This device includes an algorithm that performs analysis of patient-specific data (e.g., temperature, menstrual cycle dates) to distinguish between fertile and non-fertile days, then provides patient-specific recommendations related to contraception.

NEW REGULATION NUMBER: 21 CFR 884.5370

CLASSIFICATION: Class II

PRODUCT CODE: PYT

BACKGROUND

DEVICE NAME: Natural Cycles

SUBMISSION NUMBER: DEN170052

DATE DE NOVO RECEIVED: September 20, 2017

SPONSOR INFORMATION:

Natural Cycles Nordic AB
Luntmakargatan 26
111-37 Stockholm
Sweden

INDICATIONS FOR USE

Natural Cycles is a stand-alone software application, intended for women 18 years and older, to monitor their fertility. Natural Cycles can be used for preventing a pregnancy (contraception) or planning a pregnancy (conception).

LIMITATIONS

- Women who have been on hormonal birth control within 60 days prior to using Natural Cycles have a higher risk of becoming pregnant when compared to women who have not been on hormonal birth control within the 12 months prior to using the device.

- This device may not be right for women who have a medical condition where pregnancy would be associated with a significant risk to the mother or the fetus.

Warnings

- No method of contraception is 100% effective.
- Even when using the application perfectly, you can still have an unintended pregnancy.

Precautions

- As a contraceptive, Natural Cycles may be less suitable for you, if you have irregular menstrual cycles (cycles with length less than 21 days or greater than 35 days) and/or fluctuating temperatures, as predicting fertility is more difficult in these circumstances.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

Natural Cycles is an over-the-counter web and mobile-based standalone software application that monitors a woman's menstrual cycle using information entered by the user and informs the user about her past, current and future fertility status. The following information is entered into the application by the user:

- daily basal body temperature (BBT) measurements
- information about the user's menstruation cycle (i.e., start date, number of days)
- optional ovulation or pregnancy test results

A proprietary algorithm evaluates the data and returns the user's fertility status.

Natural Cycles is available in three modes: Contraception, Conception, and Pregnancy. Each mode is described below.

Contraception (Prevent Mode)

When the application is used for contraception, the user selects Prevent Mode, and the fertility status results are displayed in red or green colors:



Green = Not fertile

Green days indicate you are not fertile and can have sex without protection. Green days are indicated by a green outlined circle with the words "Not fertile" inside.



Red = Use protection

On red days, you are very likely to be fertile and at risk of becoming pregnant. Use protection (such as condoms or another form of barrier protection) or abstain in order to prevent a pregnancy. Red days are indicated by a red outlined circle with the words "Use protection" inside.

If the woman wants to prevent a pregnancy, she must use contraceptive protection (e.g., a condom) or abstain from intercourse on red days. Green days are days where the risk of getting pregnant due to unprotected intercourse is minimal.

Conception (Plan Mode)

When the application is used for conception, the user selects Plan Mode, and the fertility status results are displayed as a scale so that the user can easily identify the days she is most likely to become pregnant:



If a woman wants to plan a pregnancy, intercourse should be timed for during the fertile days to maximize the chance of conception. Plan Mode, which falls under product code LHD, is not within the scope of this De Novo review.

Pregnancy Mode

Natural Cycles turns into Pregnancy Mode, an optional mode, if the user is in Plan Mode and enters the results of a positive pregnancy test. The purpose of pregnancy mode is to provide educational information about the progress of the pregnancy and to enable the user to enter information to help track the status of the pregnancy. Pregnancy Mode is not within the scope of this De Novo review.

SUMMARY OF NONCLINICAL/BENCH STUDIES

SOFTWARE

Software version 3.0 was identified as having a major level of concern as defined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices," issued May 11, 2005. The software documentation included the following:

1. Software/Firmware Description
2. Device Hazard Analysis
3. Software Requirement Specifications
4. Architecture Design Chart
5. Software Design Specifications
6. Traceability
7. Software Development Environment Description
8. Revision Level History
9. Unresolved Anomalies
10. Cybersecurity

A comprehensive risk analysis was provided for the software with detailed description of the hazards, their causes and severity, as well as acceptable methods for control of the identified hazards. Natural Cycles provided a description, with test protocols including pass/fail criteria and report of results, of acceptable verification and validation activities at the unit, integration and system levels.

The cybersecurity considerations of data confidentiality, data integrity, data availability, denial of service attacks and malware were adequately addressed using application controls and procedure controls, and evidence was provided for the controls performance as intended. Risks related to failure of various software components and their potential impact on patient fertility results were also adequately addressed in the risk analysis. This software documentation information provided sufficient evidence of safe and effective software performance.

Natural Cycles has provided a full characterization of the technical parameters of the software, including a description of the algorithm that analyzes the patient's basal body temperature and menstrual cycle data to detect the day of ovulation and, by accounting for various sources of uncertainty, to determine the fertility status.

SUMMARY OF CLINICAL INFORMATION

Natural Cycles utilized real-world data to evaluate the effectiveness of the current version of the algorithm (v.3). Natural Cycles used data collected from 15,570 women age 18-45 (on average 29 years old). To be included, each woman had to be registered in the application in September to October 2017 and log at least 20 data points. Pregnancies were detected via pregnancy tests, via email follow-up or via the algorithm. Women were followed prospectively from 1 Sept 2017 to 30 April 2018, using the application for contraception, for a total exposure time of 7,353 woman-years. At the end of the study, the following commonly used failure rates were determined:

1. The application has a method failure rate of 0.6, which is a measurement of how often the application incorrectly displays a green day when the woman is actually fertile, and she gets pregnant after having unprotected intercourse on this green day. This means that 0.6 out of 100 women who use the application for one year get pregnant due to this type of failure.

2. The application has a perfect use Pearl Index of 1, which means that 1 out of 100 women who use the application for one year and who get pregnant will do so either because:
 - a. They had unprotected intercourse on a green day that was falsely attributed as non-fertile (i.e., method failure); or
 - b. They had protected intercourse on a red day, but the chosen method of contraception failed.

3. The application has a typical use Pearl Index of 6.5, which means that in total 6.5 women out of 100 get pregnant during one year of use due to all possible reasons (e.g. falsely attributed green days, having unprotected intercourse on red days, and failure of the contraceptive method used on red days).

Table 1: Summary of clinical data from 15,570 women on the effectiveness of Natural Cycles of the current algorithm version.

Algorithm	Study Date Range	# Women	Exposure (Women-years)	# Pregnancies [worst case]*	Typical use PI (95% Ci) [worst case]	Fraction of Days that were Green
V3	Sept 2017 to Apr 2018	15,570	7,353	475 [584]	6.5 (5.9-7.1) [7.9]	48.8%

*Note: Worst case assumes pregnancy in all women who left the study early with unknown pregnancy status and in all women where pregnancy was not confirmed but data indicated possible pregnancy due to delayed menstruation and consistently high temperature levels.

A retrospective analysis of patient data was conducted to validate the accuracy of the algorithm in the identification of ovulation. The ovulation day was correctly identified whether using temperature plus LH test results or just temperature alone. The performance stability of the algorithm was also demonstrated using subgroup analyses (e.g., stability over time, stability over users with recent use of hormonal birth control vs. users without recent use of hormonal birth control).

Table 2: Subgroup Analysis – Effectiveness of Natural Cycles for two subgroups - women who used hormonal contraception (HBC) within 60 days prior to using the application and women who did not use HBC within 12 months prior to using the application.

Subgroup	Typical Use PI (95% Confidence Interval)
Recent HBC (%) n=3779	8.6 (7.2-10.0)
No HBC (%) n=8412	5.0 (4.3-5.7)

Users enrolled were from 37 countries outside of the United States (OUS), the majority being from Sweden. Natural Cycles reviewed data from (b) (4) US users who were using the application for conception. It was found that menstrual cycle physiology in US users is

comparable to users in Sweden. Average temperature variation, cycle length, average number of green days, and cycle variation are consistent between US and OUS users.

An analysis evaluating the effectiveness of Natural Cycles in the subgroup of users that use the app in English compared to all users shows that the effectiveness rates are consistent between the two groups.

Table 3: Performance of women using the current version of the app in English compared to all users

Group	# Women	# Pregnancies	PI Typical use (95% CI)
English language only	10,789	295	5.8 (5.1-6.4)
All	15,570	475	6.5 (5.9-7.1)

HUMAN FACTORS

A usability study was conducted to verify that users can self-identify that they are in the intended use population and can correctly use the application. An analysis of data collected from (b) (4) users confirmed that 98.9% of these users were between the ages of 18 and 45. Only 0.1% of users were younger than 18, while 1% of users were older than 45. Even though users were enrolled from 37 OUS countries, the most commonly used language by users was English. Sixty-nine percent of users participating in the human factors study used the application and labeling in English. Therefore, although the study was conducted OUS, the study demonstrated that users can self-identify that they are in the intended use population and can correctly use the application.

To assess whether women understand that protection should be used on red days, sexual activity was tracked. A total of 29% of women using the application for contraception had sex on red days. The types of protection used by prevent mode users on red days included:

- Condom (49%)
- Withdrawal (25%)
- Abstinence (9%)
- Diaphragm / female condom (1%)
- Spermicide (1%)
- Combination of above (6%)
- No protection, taking the risk (4%)

When the respondents who said they were not using any protection on red days were asked why, the responses were:

- Trying to conceive (switch to Plan mode) (17%)

- Confirmed that they were actually using withdrawal (47%)
- Confirmed that they used no protection and were taking the risk (19%)
- Had an IUD in place (5%)
- Sex was not penetrative (2%)
- Did not know that red meant fertile (2%)
- Other reason, not specified (8%)

The responses confirmed that a very high percentage of users understand that some form of contraception should be used on red days unless trying to get pregnant or affirmatively taking the risk.

A comparison of pregnancy rates for prevent mode users (i.e., application being used for contraception) and plan mode users (i.e., application being used for conception) also demonstrates that the users understand the labeling. The results show that prevent mode users have a very low pregnancy rate while plan mode users have a high pregnancy rate. This helps demonstrate that the control of conception is achieved by how users behave based on the labeling and that the labeling information regarding how to prevent pregnancies is clear.

The results are generalizable to a US population for several reasons:

- The education level of users in the US is slightly better than in the rest of the world (85% of users have at least a university degree).
- The users are of similar ages (30 years on average).
- The average temperature variation recorded by US users is the same as OUS users, which indicates that US women can correctly measure and enter their basal body temperatures.
- The average cycle length recorded by US users is the same as OUS users, which shows that US women can understand when and how to enter menstruation data (and that their cycle characteristics are similar).

Pediatric Extrapolation

The device is indicated for women 18 years and older only. The Federal Food, Drug, and Cosmetic Act defines pediatric patients as persons aged 21 or younger. In this De Novo request, existing clinical data were not leveraged to support the use of the device in women younger than 18 years old.

LABELING

The labeling is provided in the form of an Instructions for Use manual. The Instructions for Use can be downloaded by the user on the Natural Cycles Nordic AB's public website at any time and can be accessed directly from within the application. Information from the labeling is also provided within the application as text, messages, or in pop-up boxes.

The device labeling is for women 18 years and older. The labeling specifies the intended user population, instructions on how to use the application, and guidance for safe and effective use of the device.

The product warnings and precautions included in the labeling specify factors that may impact the accuracy of the fertility determinations and behavior required when the application identifies the user as fertile. The warnings also indicate that no contraceptive method is 100% effective, and the application cannot protect against sexually transmitted infections.

The labeling also provides a summary of the clinical validation study and results. This summary includes a comparison of the device efficacy to other forms of legally marketed contraceptives.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with use of the software application for contraception and the measures necessary to mitigate these risks.

Identified Risk	Mitigation Measures
Unintended pregnancy	Software verification, validation, and hazard analysis; Clinical performance testing; Human factors and usability testing; and Labeling

SPECIAL CONTROLS

1. Clinical performance testing must demonstrate the contraceptive effectiveness of the software in the intended use population.
2. Human factors performance evaluation must be provided to demonstrate that the intended users can self-identify that they are in the intended use population and can correctly use the application, based solely on reading the directions for use for contraception.
3. Software verification, validation, and hazard analysis must be performed. Documentation must include the following:
 - a. A cybersecurity vulnerability and management process to assure software functionality; and
 - b. A description of the technical parameters of the software, including the algorithm used to determine fertility status and alerts for user inputs outside of expected ranges.
4. Labeling must include:
 - a. The following warnings and precautions:
 - i. A statement that no contraceptive method is 100% effective.

- ii. A statement that another form of contraception (or abstinence) must be used on days specified by the application.
 - iii. Statements of any factors that may affect the accuracy of the contraceptive information.
 - iv. A warning that the application cannot protect against sexually transmitted infections.
- b. Hardware platform and operating system requirements.
 - c. Instructions identifying and explaining how to use the software application, including required user inputs and how to interpret the application outputs.
 - d. A summary of the clinical validation study and results, including effectiveness of the application as a stand-alone contraceptive and how this effectiveness compares to other forms of legally marketed contraceptives.

BENEFIT-RISK DETERMINATION

The risks of the device are based on data collected in the clinical study described above. The typical use Pearl Index of Natural Cycles is 6.5. This means that out of 100 women using the device for contraception for one year, 6.5, or approximately 7 women, will have an unintended pregnancy. Users must be aware that even with consistent use of the device, there is still a possibility of unintended pregnancy.

The probable benefits of the device are also based on data collected in the clinical study described above. The probable benefit of Natural Cycles is that it offers an alternate method of contraception, which is non-hormonal, and will appeal to users who wish to avoid hormones. For optimal use, it requires information to be entered into the application by the user. For this reason, it may also appeal to users in that they will feel more “in control” of their contraception. It also can be initiated without a visit to the doctor, as it is for over the counter use.

Patient Perspectives

Patient perspective data were collected as part of the usability study and clinical performance data; however, these data were not specific to contraceptive effectiveness and therefore were not used to assess the safety and effectiveness of the device.

BENEFIT/RISK CONCLUSION

In conclusion, given the available information above, for the following indication statement:

Natural Cycles is a stand-alone software application, intended for women 18 years and older, to monitor their fertility. Natural Cycles can be used for preventing a pregnancy (contraception) or planning a pregnancy (conception).

the probable benefits outweigh the probable risks for the Natural Cycles device. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Natural Cycles is granted and the device is classified as follows:

Product Code: PYT

Device Type: Software application for contraception

Class: Class II

Regulation Number: 21 CFR 884.5370