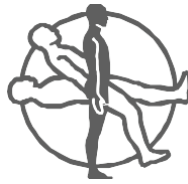


Medtronic

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| Study Title | A multi-center observational study during pregnancy for women with T1DM treated with the Paradigm insulin pumps donated by the 'Wielka Orkiestra Świątecznej Pomocy' Foundation in Poland |
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**Medtronic***Alleviating Pain · Restoring Health · Extending Life*

A multi-center observational study
during pregnancy for women with T1DM
treated with the Paradigm insulin pumps
donated by the 'Wielka Orkiestra
Świątecznej Pomocy' Foundation in
Poland

Clinical Investigation Plan

Version 4.0

18Mar2015

PL01

| Sponsor |
|--|
| Medtronic Poland ul. Osrobramska 101 04-041 Poland Poland |

Change History record

| CIP Change History | | |
|--------------------|---|------------|
| Version | Summary of Changes | Author |
| Version 1.0 | Initial release | ██████████ |
| Version 2.0 | A, D. 1 – Inclusion criteria: “Subject having a male partner” deleted B. 2 – Use of preferred / accepted BG meters explained E. 5 – Information on current reimbursement status of CSII and CGM in Poland added F. 2 – Patient questionnaires: DTSQ added, HFS timelines adjusted G. 1. 3 – Priority of source data review adjusted G. 2 – Medtronic monitors’ responsibility specified Wording and text adjustments | ██████████ |
| Version 3.0 | A, Treatment – sensor use A, B.2 – device certificate references removed A., D.1, D. 2 Inclusion/Exclusion criteria – wording adjustments, “Use of contraception during insulin pump therapy” deleted; Adjustment of endpoints A. Planning phase extended from 6 to 12 months C. 7 – Adjustment of study timelines F. 2, F. 3 – Extension of planning phase from 6 to 12 months F. 3 – ‘Microalbumin/creatinin’ replaced by ‘Albumin/creatinine’ F. 4 – ‘Role of sponsor representatives’ added H. 1 – Detailed ‘Analysis of clinical data’ added H. 2 – ‘Publication policy’ adjusted I. 2 – ‘Advisory committees’ adjusted L. 1 – Names and addresses updated Wording adjustments based on new CIP template | ██████████ |
| Version 4.0 | Author – new Study Manager A. “CSII and SAP: replaced by “CSII including SAP”, duration of enrolment period, “Sensor compliance” deleted C. “CSII and/or SAP: replaced by “CSII including SAP” C. 3 New wording C.7 Updated timelines H. 1 Adjusted wording | ██████████ |

TABLE OF CONTENTS

| | | |
|---|--|----|
| A | SYNOPSIS | 8 |
| B | GENERAL INFORMATION | 12 |
| | B.1 Introduction | 12 |
| | B.2 Device information | 14 |
| C | STUDY PLAN | 16 |
| | C.1 Study objectives | 16 |
| | C.1.1 Primary objectives | 16 |
| | C.1.2 Secondary objectives | 16 |
| | C.2 Clinical endpoints | 16 |
| | C.2.1 Maternal outcomes | 16 |
| | C.2.2 Delivery information | 17 |
| | C.2.3 Neonatal outcomes | 17 |
| | C.3 Study hypothesis | 18 |
| | C.4 Study population | 18 |
| | C.5 Study design | 18 |
| | C.6 Sample size | 18 |
| | C.7 Number of investigation sites and study duration | 18 |
| D | SUBJECT SELECTION | 19 |
| | D.1 Inclusion criteria | 19 |
| | D.2 Exclusion criteria | 19 |
| E | STUDY PREPARATION PROCEDURES | 20 |
| | E.1 Investigator/Investigation site selection | 20 |
| | E.1.1 Clinical Investigation Agreement | 20 |
| | E.2 Ethics | 20 |
| | E.2.1 EC/IRB approval | 20 |
| | E.2.2 Informed consent process | 20 |
| | E.2.3 Revisions in Patient Information and Informed Consent Form | 21 |
| | E.2.4 Regulatory notification / approval | 21 |
| | E.3 Regulatory compliance | 21 |
| | E.4 Training requirements | 21 |
| | E.5 Study materials and study-specific equipment | 21 |
| | E.6 Study device/product traceability | 21 |
| F | STUDY METHODS | 22 |
| | F.1 Point of enrollment | 22 |
| | F.2 Implant or procedure aspects | 22 |
| | F.3 Data collection requirements | 28 |
| | F.4 Role of the sponsor's representatives | 37 |
| | F.5 Source documents | 37 |
| | F.6 Adverse events | 37 |
| | F.6.1 Definitions | 37 |
| | F.6.2 Recording and reporting of Serious Adverse Events | 39 |

| | | |
|---|---|----|
| | F.6.3 Post Market Surveillance | 40 |
| | F.6.3.1 Definition/classification | 40 |
| | F.6.3.2 Reporting of product complaints | 40 |
| | F.7 Subject accountability | 40 |
| | F.8 Study deviations and CIP changes | 41 |
| | F.8.1 Request for approval of study deviations | 41 |
| | F.8.2 Reporting requirements for study deviations | 42 |
| | F.8.3 Amendments to the Clinical Investigation Plan | 42 |
| G | QUALITY CONTROL PROCEDURES | 42 |
| | G.1 Procedures for database management | 42 |
| | G.1.1 Data collection | 42 |
| | G.1.2 Time windows for completion and submission of Case Report Forms | 42 |
| | G.1.3 Data review and processing | 43 |
| | G.2 Monitoring procedures | 43 |
| | G.2.1 Accessibility of investigation site staff and study materials | 43 |
| | G.2.2 Audits and investigation site inspections | 43 |
| | G.3 Study suspension or early termination | 44 |
| | G.3.1 Early study suspension or termination | 44 |
| | G.3.2 Early investigation site suspension or termination | 44 |
| | G.3.3 Subject follow-up in case of termination | 44 |
| | G.4 Study close out | 44 |
| H | DATA ANALYSIS AND REPORTING | 45 |
| | H.1 Analysis of clinical data | 45 |
| | H.1.1 Analysis of Primary Objectives | 45 |
| | H.1.2 Analysis of Secondary Objectives | 46 |
| | H.2 Publication Policy | 48 |
| I | STUDY MANAGEMENT | 49 |
| | I.1 Study staff | 49 |
| | I.2 Advisory committees | 49 |
| | I.2.1 Publication Committee | 49 |
| | I.3 Records and reports | 49 |
| | I.3.1 Investigator records | 49 |
| | I.3.2 Investigator reporting responsibilities | 49 |
| | I.3.3 Sponsor records | 49 |
| | I.3.4 Sponsor reporting responsibilities | 50 |
| | I.3.5 Record retention | 50 |
| | I.4 Miscellaneous | 50 |
| | I.4.1 Subject compensation and indemnification | 50 |
| | I.4.2 Subject confidentiality | 50 |
| J | RISKS AND BENEFITS | 50 |
| | J.1 Anticipated Clinical Benefits | 50 |
| | J.2 Risks | 51 |
| K | REFERENCES | 51 |
| L | APPENDICES | 53 |



| | | |
|-------|---|----|
| L.1 | Names and addresses..... | 53 |
| L.1.1 | List of contact persons..... | 53 |
| L.1.2 | List of participating investigation sites and investigators | 54 |
| L.2 | Case Report Forms | 54 |
| L.3 | Patient Questionnaires | 54 |
| L.4 | Abbreviations | 54 |

A SYNOPSIS

Title: A multi-center observational study during pregnancy for women with T1DM treated with the Paradigm insulin pumps donated by the 'Wielka Orkiestra Świątecznej Pomocy' Foundation in Poland

Short title: Orchestra Pregnancy Observational Study in Poland

Purpose

The aim of this project is to document the use of insulin pump therapy (CSII), including sensor augmented pump therapy (SAP), before, during and after pregnancy in women with type 1 Diabetes Mellitus benefiting from the Orchestra donation of Paradigm REAL-Time and Paradigm Veo pumps in Poland.

Objectives

To assess the benefits of CSII, including SAP, on the maternal glycemic control (HbA1c and Continuous Glucose Monitoring data)

To assess the prevalence of pregnancy complications (rates of preterm delivery, infant birth weight, neonatal care admissions) from preconception phase, throughout pregnancy, during delivery and after delivery during lactation phase (up to 6 weeks). To report and assess the potential benefits of SAP or CSII on neonatal outcomes

Indication

Pregnancy with Type 1 Diabetes Mellitus

Medical devices

The devices to be used in the study are the Paradigm REAL-Time (722) insulin pump, including the sensor augmented Paradigm® Veo (754) system (insulin pump + Enlite sensor + MiniLink transmitter); all devices are CE-marked and manufactured by Medtronic. All devices are commercially released and used within their intended use. They are available and labelled in the local language as are the Instructions for Use.

- Paradigm® REAL-Time 722 insulin infusion pump (MMT-722)
- Paradigm® VEO™ Insulin Pump (MMT-754)
- Enlite® Sensor (MMT-7008) Enlite® Serter (MMT-7510)
- MiniLink™ Transmitter (MMT-7703)
- MiniLink™ Charger (MMT-7705) CareLink® USB (MMT-7305)
- Medtronic CareLink® Clinical Therapy Management Software for Diabetes (MMT-7334)
- Bayer® Contour Link™ BG Meter
- Another model or brand of BG Meter that is compatible with the CareLink Clinical software, if Bayer® Contour Link™ BG Meter is not available

Except for Enlite sensors that are for single use, all the devices are loaned to the study participants for the study period, and will be returned to the investigation site, and will be used by other eligible subjects.

Design

The project is designed as a multi-center prospective observational Post-Market-Release study to be conducted in up to 30 centers in Poland.

Total duration of the study per patient will be up to 22 months (up to 12 months pre-conception phase, pregnancy, and 6 weeks after delivery). The optimal study start is the beginning of pre-conception phase, however, pregnant women up to the 16th week of pregnancy can participate in the study too. The study end is 6 weeks after delivery. If conception does not occur within 12-months, the patient's study participation is terminated, and the insulin pump might be taken away from the patient. The following therapy is decided by the investigator. If the pump is not taken away after the 12-month of trial period for conception, the patient can continue insulin pump therapy until the pump is needed for another patient.

The study started in May 2013; enrolment period is planned for 30 months which can be modified by the decision of the Steering Committee. The final report will be available within 24 months after the end of enrolment.. Data collection will be stopped when data have been collected from 100 pregnancies with complete follow-up (including pre-conception phase, pregnancy, delivery and 6 weeks of lactation).

Treatment

- Approximately 2/3 of the study subjects will be provided with the Paradigm REAL-Time (stand-alone pump therapy, CSII), and rest of the subjects will be provided with the Paradigm Veo, MiniLink transmitter and sensors (sensor augmented pump therapy - SAP). The decision about the type of treatment is made by the Health Care Professional (HCP) together with the patient independently of the study. It is advised to choose sensor augmented pump therapy for patients who present overall good compliance and ability to understand and use such a therapy, as assessed by the treating physician.
- MiniLinks and sensors are provided free of charge mainly to Paradigm Veo users, from the pre-conception period until one month after delivery, ideally with wearing the sensor during delivery. For all planned deliveries with the sensor-augmented Paradigm pumps, the sensor should be ideally started 2 to 3 days before the delivery.
- Patients on the sensor-augmented Paradigm pumps can get as many sensors free of charge as recommended by their HCPs.
- Patients on the Paradigm REAL-Time without free of charge MiniLinks donated by the Orchestra Foundation can use Continuous Glucose Monitoring (MiniLink and sensors) to their own desire and costs, if agreed with the HCP.
- Patients attend regular routine follow-up without special requirements, where medical information is being collected in the eCRF system and the data from devices (pumps and meters) is being uploaded into CareLink Clinical.
- Women with miscarriage can keep their pump for additional 3 months after the miscarriage, if they want to continue the therapy.

Subject Population

The study will collect data until a minimum of 100 pregnancies with full follow-up on CSII or SAP are completed including the pre-conception period, pregnancy, and 6 weeks after delivery. The expected number of subjects to be enrolled is 500 in 30 diabetes centers in Poland, so that data from 100 pregnancies with complete follow-up could be collected. The study will stop when the 100 complete pregnancies have been completed, and followed up until 6 weeks after delivery.

Subject's participation will include up to 6 visits in up to 22 months for subject enrolled at the planning stage and followed until 6 weeks after delivery.

Inclusion Criteria

A subject is eligible for the study if the following criteria are met:

- Female diagnosed with Diabetes Mellitus Type 1
- Subject indicated by HCP to start insulin pump therapy (CSII) or sensor augmented pump therapy (SAP) due to the desired or established pregnancy
- HCP has prescribed the use of Orchestra donated device to the subject independently of the study
- Signed Patient Informed Consent (PIC)
- Subject is 18 to 45 years old, planning immediate pregnancy (within the next 12 months) or being pregnant within the first trimester until the 16th week of amenorrhea
- Subject has been on MDI for at least 3 months before starting pump therapy

Exclusion Criteria

A subject is excluded from the study if any of the following criteria are met:

- Subject was enrolled in the registry earlier, and terminated it (for any reason)
- Participation in any other interventional clinical trial – currently and/or in the last 3 months before the signature of PIC
- Subject uses an insulin pump that was not donated by the Orchestra foundation
- Pregnant women with longer than 16 weeks of pregnancy/amenorrhea
- Subjects who need assisted in vitro fertilization
- Subjects with Diabetes Mellitus Type 2, Gestational Diabetes, MODY or any other type of diabetes than Type 1
- Subject under the age of 18
- Subject legally incompetent
- Subject cannot read or write

Endpoints

Data will be collected during routine follow-up visits from pre-conception time, during pregnancy and delivery, up to 6 weeks after delivery and at miscarriage, if any. Some endpoints as described below will be collected from patient medical files retrospectively up to 12 months prior to study start.

Maternal outcomes

- HbA1c (local laboratory) – last value before insulin pump therapy started (retrospective value from patient's medical file), 2-3 values during pregnancy, and one value at the end of the study.
- Proportion of women achieving HbA1c <6.0%, 6.5%, 7%, 7.5% and 8% at each trimester
- Serious adverse events
 - Severe hypoglycaemia (according to the standard definition requiring third party assistance – see point F 5. 1) from the period of 12 months prior to study start until study end
 - DKA from the period of 12 months prior to study start until study end
 - Miscarriage, hospitalization because of uterine bleeding, hospitalization because of instable glycaemia and others
 - Any hospital admission
- Weight, BMI
- Daily insulin use
- Medical information: Microalbumin excretion with albumin/creatinin ratio, blood pressure, parity, folic acid and any other supplementation, White classification, diabetes duration, previous insulin regimen
- Number of SMBG/day (patient self-reported)

- - Patient questionnaires:
 - Hypoglycaemia Fear Survey (HFS) collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery
 - Diabetes Treatment Satisfaction Questionnaire (DTSQs, status version), collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery, and Diabetes Treatment Satisfaction Questionnaire (DTSQc, change version), collected at 24 weeks into pregnancy
 - Device Data:
 - Descriptive statistics for SMBG and SG (mean, SD, median, min and max)
 - time spent SG < 50 mg/dL
 - time spent SG between 50-70 mg/dL
 - time spent SG between 70-120 mg/dL
 - time spent SG between 120-140 mg/dL
 - time spent SG > 140 mg/dL
 - time spent SG > 180 mg/dL
 - AUC (SG < 70 mg/dl, SG > 180 mg/dl)
 - MAGE
 - All these parameters daily, 2-hour postprandial and during night (10PM to 7AM)
 - Pump Compliance
 - Sensor Compliance, if necessary.

Delivery information

- Sensor and pump wear during delivery (yes/no)
- Patient satisfaction with treatment during delivery

Neonatal outcomes

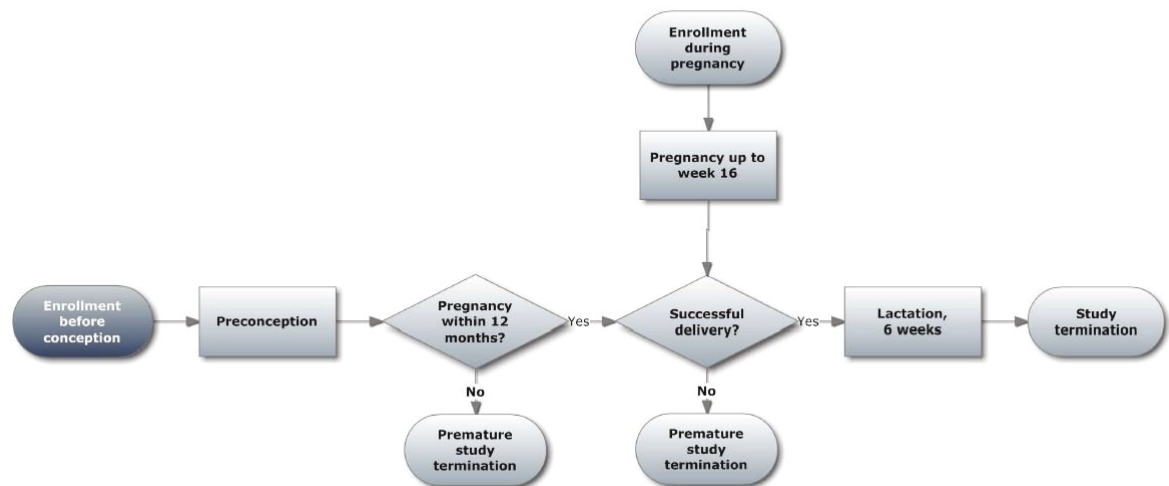
- Mode of delivery (rates elective and emergency Caesarean Section, normal)
- Respiratory distress (1 and 5 minute Apgar scores)
- Gestational age at delivery, % preterm delivery < 37 weeks
- Infant birth weight (SD scores and customised birth weight percentile, % large for gestational age (LGA), % small for gestational age (SGA))
- Neonatal morbidity (treatment for neonatal hypoglycaemia)
- Neonatal care admission (duration of stay, level of care)
- Pregnancy related Serious Adverse Events (miscarriage < 22 weeks, congenital malformation, stillbirth, neonatal death)
- Feeding at hospital discharge (breast, bottle, both)

Timing of data collection into eCRF:

- Baseline
- End of conception trial or after 12 months
- Pregnancy start
- 3 months of pregnancy (12 weeks of amenorrhea \pm 4 weeks)
- 6 months of pregnancy (24 weeks of amenorrhea \pm 2 weeks)
- 9 Months of pregnancy (36 weeks of amenorrhea \pm 2 weeks)
- Delivery (+ 2 weeks)
- 6 weeks after delivery (\pm 2 weeks)
- Miscarriage any time

Clinical Procedures

Figure 1: Flow chart of the Enrollment and Termination possibilities depending on the pregnancy



B GENERAL INFORMATION

B.1 Introduction

Diabetic pregnancies are associated with considerable risks for both the woman and the fetus. Risks for the woman include miscarriage, hypoglycaemia, ketoacidosis, pre-eclampsia, premature labour, polyhydramnios and obstructed labour, with increased rates of instrumental delivery and caesarean section. Babies are at increased risk of congenital malformation and macrosomia with consequent increased rates of perinatal mortality, birth injuries, neonatal hypoglycaemia, jaundice and respiratory distress.¹⁻⁹

High-quality cohort studies have established the relation between glucose control before conception and the incidence of miscarriage and congenital malformations¹⁰. High HbA1c levels in early^{1,2,4-8} and late³ pregnancy are associated with these risks and complications. Congenital malformations and the risk of miscarriage increases as first-trimester HbA1c increases above the normal range, and evidence shows that hyperglycaemia during pregnancy are associated with fetal macrosomia (and associated birth injury and caesarean sections) and fetal morbidity.¹⁰ A hyperglycaemic intrauterine environment, may also predispose the child to Type 2 diabetes or pre-diabetes^{11,12} and to being overweight.¹²

Achieving tight glucose control throughout pregnancy is challenging. A UK study showed pregnancies treated with multiple daily injections (MDI) spend eight to ten hours per day with glucose levels above the recommended range¹³ resulting in a 3-5 times greater rate of major congenital malformation, stillbirth and neonatal death than seen in the background maternity population^{4,14}. For those pregnancies delivering “healthy” live born infants, 66% are delivered by caesarean section, 50% are large for gestational age, 37% are delivered preterm and 40% are admitted to neonatal intensive care¹⁵. Interestingly in Germany, where insulin pump

therapy (CSII) use is common, pregnancy outcomes have improved in recent years with decreases in stillbirths, premature delivery and macrosomia,¹⁶ which the authors relate to improved diabetic rather than obstetric care.

The strict glycaemic control needed to ameliorate the risk of complications is challenged factors such as undetected post-prandial hyperglycaemia and overnight hypoglycaemia¹⁷ and an increased risk of severe hypoglycaemia¹⁸. Studies have shown that improvements in HbA1c are achieved but were associated with increases in hypoglycaemia^{19,20}.

Severe hypoglycaemia (SH), accompanied by unconsciousness, convulsions and hospitalization²¹⁻²³, is a feared condition among non-pregnant subjects with diabetes²⁴, and affects women in particular²⁵. Yet SH affects between 25-40% mothers²⁶ and is three to five times as frequent in early pregnancy as in the period prior to pregnancy^{21,22}. Rates of SH in the late first and early second trimester showed an increase of 16%²⁷, and in an intensively treated group subjects had 15 times more SH than the conventionally treated group²⁸. Nocturnal hypoglycaemia is also common in the first trimester, with a 37% prevalence shown by hourly venous sampling between 22:00h-07:00h²⁹. Ironically, during pregnancy, hypoglycaemia is less harmful to the fetus than to the mother³⁰, but hyperglycaemia poses increased risks for the fetus. Therefore, from the perspective of fetal outcomes, strict metabolic control in early pregnancy must still be advocated, but other means for preventing severe hypoglycaemia should be implemented³¹.

CSII in non-pregnant Type 1 subjects was associated with a reduced rate of severe hypoglycaemia without adversely affecting glycaemic control when compared with MDI therapy³⁰. There is recent convincing evidence from multicenter randomised controlled trials (RCT) that both CSII and continuous glucose monitoring (CGM) independently, or in combination as sensor-augmented pump therapy (SAP) improve glycaemic control by decreasing HbA1c in the range of -0.43% to -1.2%³²⁻³⁸. An RCT of 71 pregnancies complicated with diabetes had an end-of-pregnancy improvement of -0.6% and reduced risk of macrosomia when using CGM¹³.

Postprandial blood glucose levels have a stronger association with incidence of macrosomia than HbA1c. Two RCTs found that monitoring of post-prandial glucose levels produced better outcomes than pre-prandial monitoring¹⁰. Neonatal outcomes are more closely associated with hyperglycaemic excursions than with the average glycaemic control³⁹⁻⁴¹. The frequency, magnitude and duration of hyperglycaemic excursions, are best captured by CGM¹³ which has an accuracy comparable to gold standard plasma glucose measurements in pregnancy⁴¹ yet provides continuous information on glucose levels. Indeed, analysis of CGM for hyperglycaemia may be a useful marker of anticipated neonatal outcomes⁴³.

The prevention of severe hypoglycaemia has been demonstrated with CGM-related features such as alarms⁴⁴, and automatic insulin suspension (LGS)^{45,46}. The use of CGM reduced the incidence of SH by 32.8% in adults⁴⁷ and the LGS feature reduced SH by 46% in children⁴⁵ and 69% in a mixed population⁴⁶. Inappropriate treatment of hypoglycaemia may result in hyperglycaemia, but when the LGS feature was triggered in response to hypoglycaemia, there was no rebound hyperglycaemia observed⁴⁸. In addition to a decrease in SH events, CGM also reduces the time spent in the hypoglycaemia range^{38,49,50,51} and effectively reduced the fear of hypoglycaemia and the fear of severe hypoglycaemia⁴⁷.

In conclusion, the management of diabetes during pregnancy needs to ensure an appropriate HbA1c is attained before and during pregnancy while reducing the mothers' exposure to hypoglycaemia and severe hypoglycaemic events, and reducing the fetus' exposure to hyperglycaemia. Sensor-augmented pump therapy provides the technology to enable reductions of HbA1c, to anticipate and alert the mother to glucose levels outside the target range, and to assist in preventing severe-hypoglycaemic events without the risk of rebound hyperglycaemia.

In 2012, the Orchestra Foundation (Fundacja Wielka Orkiestra Świątecznej Pomocy) decided to fund Insulin Pump Therapy (CSII) for pregnant women in the pre-conception period, during pregnancy and six weeks after delivery in Poland. The foundation also covers sensor use for

about 1/3 of the study participants during the pregnancy period (SAP – Sensor Augmented Pump). Orchestra has requested that a professional data collection is organized from the patients who benefit from this donation in all investigation sites that received the donated devices. Medtronic is engaged in creating the design of the registry as well as in the data management that will allow publication of the results in a journal/journals to be selected by the Publication Committee.

B.2 Device information

All devices used in this study are CE-marked and manufactured by Medtronic. They are available and labelled in the local language as are the Instructions for Use.

- **Paradigm® REAL-Time 722 insulin infusion pump (MMT-722)**

or

- **Paradigm® Veo™ Pump (MMT-754 or MMT-554)**

The Medtronic Minimed Paradigm® REAL-Time insulin pump and continuous glucose monitoring system (PRT system) and the Medtronic Minimed Paradigm® Veo and continuous glucose monitoring system (Veo system) are the devices used in this study.

The PRT System and the Veo system have been developed for people with diabetes and are based on Medtronic's Paradigm series of insulin pumps and the CGMS/Guardian series of continuous glucose monitoring systems. The PRT system and the Veo system have been designed to allow the patient to wear one device performing two important functions: **delivering insulin** and **continuously measuring glucose**.

The face of the pumps provides the user with push pad pump controls and a data screen for viewing continuous real-time glucose values, glucose trends, alerts, alarms and other information set according to the individual patient's needs. The pump is capable of receiving radio signals from a glucose sensor transmitter, which will be connected to the ENLITE sensor and MiniLink GST during this study. Pump data will be uploaded using CareLink USB to Medtronic CareLink Clinical software. The intended use is to deliver insulin by subcutaneous infusion to diabetes patients. Medtronic is the legal manufacturer of this device.

- **Enlite® Sensor (MMT-7008),**

The Enlite sensor continuously converts tiny amounts of glucose from the fatty layer under the skin into an electronic signal. This signal is sent to the transmitter. The sensor includes a microelectrode with a thin coating of glucose oxidase beneath several layers of biocompatible membrane. It is intended to penetrate the skin at a 90-degree angle. An introducer needle penetrates the skin surface and provides support for the sensor microelectrode during insertion.

The sensor continuously converts small amounts of glucose from the subject's interstitial fluid into an electronic signal that is received by a transmitter or recorder, the strength of which is proportional to the concentration of glucose in the interstitial fluid. The electrode is composed of embedding, signal-conducting and insulating layers. The sensor has an adhesive extension that secures the free end of a glucose sensor transmitter or glucose sensor recorder. Medtronic is the legal manufacturer of the Enlite sensors. The intended use is to measure interstitial glucose levels in the subcutaneous tissue.

- **Enlite® Serter (MMT-7510)**

The Enlite serter is used to ensure correct placement of the Enlite sensor. The Enlite serter inserts the sensor at a 90-degree angle and injects the sensor into the insertion site when the button is released. The Enlite serter also minimizes sharps exposure, facilitates adhesive cover removal, and supports one hand insertion without visual access. The Enlite serter is intended

for single patient, multi-use device. The Enlite senter is manufactured by Medtronic. Its intended use is to insert the Enlite sensor.

- **MiniLink™ Transmitter (MMT-7703)**

The Medtronic MiniLink™ transmitter (MiniLink) is a component of continuous glucose sensing systems and sensor augmented insulin pump systems. The MiniLink powers the glucose sensor, collects glucose data, and wirelessly sends the data to a monitor. The monitor is a Medtronic continuous glucose sensing monitor or Medtronic MiniMed® sensor augmented insulin pump. The MiniLink Transmitter is part of the MiniLink system, manufactured by Medtronic. The intended use is to transmit data to the Medtronic insulin pump.

- **MiniLink™ Charger (MMT-7705)**

The charger is used to recharge the MiniLink battery as needed. The charger is powered by a AAA battery intended to last for up to four months, and is designed for easy connection and disconnection from the MiniLink. The charger has a green light that shows the charging status and a red light that communicates any problems during charging. The full recharge lasts for up to 14 days of continuous use. After 14 days of use, the MiniLink can be fully recharged in less than 1 hour. The MiniLink charger is part of the MiniLink system, manufactured by Medtronic. The intended use is to charge the MiniLink.

- **CareLink® USB (MMT-7305)**

The Medtronic CareLink USB, is indicated for use commercially by patients at home and for clinicians in a medical office setting as a means of facilitating communication between Medtronic diabetes therapy management devices that use Paradigm-compatible RF telemetry and a personal computer that uses data management application software. The CareLink USB device will enable data from the pump to be uploaded to CareLink Clinical. The CareLink USB is part of the CareLink system, manufactured by Medtronic. The intended use is to connect the pump to a computer for data upload.

- **Medtronic CareLink® Clinical Therapy Management Software for Diabetes (MMT-7334),**

Medtronic CareLink® Clinical Therapy Management Software is a Web-based system which allows the device data to be viewed and easily evaluated by the subject and his/her physician. A PC links to the Medtronic CareLink® system via the Internet and allows the subject to upload data from Medtronic MiniMed insulin pump and third-party blood glucose meters. The clinical support version of Medtronic CareLink may be used by clinical trial subjects or Investigational Center staff. For the purposes of this study, uploads are performed only by the investigational center staff.

All references to CareLink are meant to imply the clinical support version of Medtronic CareLink and throughout the protocol will be referred to as CareLink. The data contained in CareLink is accessible to users using a standard browser, i.e., Microsoft® Internet Explorer, on an Internet enabled PC.

The CareLink Clinical system uses standard Secure Socket Layer (SSL) technology.

SSL transmission protocol invokes encryption on both ends of the transmissions and is the standard for all security based systems. The encryption remains in effect whether the data is moving to and from the client and server in the United States, or to and from a client in another country to the United States. The data is secure behind a three tier industry standard architecture, which places the database behind three different firewalls, where each firewall separates a tier:

- The internet to the web server;
- Web server to the application server;

- Application server to the database server.

These uploads will be used by Medtronic for data collection and analysis.

The intended use of CareLink is to upload data from an insulin pump to the on-line clinical database. Medtronic is the legal manufacturer of this device.

- **Bayer® Contour Link™ Meter**

The Contour Link blood glucose meter is manufactured by Bayer Inc. The meter determines the subject's capillary blood glucose level. The blood glucose values are stored by the meter and can be uploaded into CareLink Clinical. The intended use is to measure blood glucose levels and transmit the values into the Paradigm insulin pump. By uploading the insulin pump into CareLink Clinical the blood glucose values get uploaded too.

C STUDY PLAN

C.1 Study objectives

The aim of this study is to document the use of insulin pump therapy (CSII), including sensor augmented pump therapy (SAP), before, during and after pregnancy in women with Type 1 Diabetes Mellitus benefiting from the Orchestra donation of Paradigm REAL-Time and Paradigm Veo pumps in Poland.

C.1.1 Primary objectives

To assess the benefits of CSII, including SAP, on the maternal glycemic control (HbA1c and Continuous Glucose Monitoring data)

C.1.2 Secondary objectives

To assess the prevalence of pregnancy complications (rates of preterm delivery, infant birth weight, neonatal care admissions) from preconception phase, throughout pregnancy, during delivery and after delivery during lactation phase (up to 6 weeks)

To report and assess the potential benefits of CSII, including SAP, on neonatal outcomes

To evaluate change in patient-reported outcomes using the Hypoglycemia Fear Survey (HFS) and the Diabetes Treatment Satisfaction Questionnaire (DTSQs and DTSQc)

C.2 Clinical endpoints

Data will be collected during routine follow-up visits from pre-conception time, during pregnancy and delivery, up to 6 weeks after delivery and at miscarriage, if any,. Some endpoints as described below will be collected from patient medical files retrospectively up to 12 months prior to study start.

C.2.1 Maternal outcomes

- HbA1c (local laboratory) – last value before insulin pump therapy started (retrospective value from patient's medical file), 2-3 values during pregnancy, and one value at the end of the study. Calibration needed for the analysis
- Proportion of women achieving HbA1c < 6.0%, 6.5%, 7%, 7.5% and 8% at each trimester
- Serious adverse events

- Severe hypoglycaemia (according to the standard definition requiring third party assistance – see point F 5. 1) from the period of 12 months prior to study start until study end
- DKA from the period of 12 months prior to study start until study end
- Miscarriage, hospitalization because of uterine bleeding, hospitalization because of instable glycemia and others
- Any hospital admission
- Weight, BMI
- Daily insulin use
- Medical information: Microalbumin excretion with albumin/creatinin ratio Blood pressure, parity, folic acid and any other supplementation, White classification, diabetes duration, previous insulin regimen
- Number of SMBG/day (patient self-reported)
-
- Patient questionnaires:
 - Hypoglycaemia Fear Survey (HFS) collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery
 - Diabetes Treatment Satisfaction Questionnaire (DTSQs, status version), collected at enrollment, 2-3 x during pregnancy, and 6 weeks after delivery, and Diabetes Treatment Satisfaction Questionnaire (DTSQc, change version), collected at 24 weeks into pregnancy.
- Device Data:
 - Descriptive statistics for SMBG and SG(mean, SD, median, min and max)
 - time spent SG < 50 mg/dL
 - time spent SG between 50-70 mg/dL
 - time spent SG between 70-120 mg/dL
 - time spent SG between 120-140 mg/dL
 - time spent SG > 140 mg/dL
 - time spent SG > 180 mg/dL
 - AUC (SG < 70 mg/dl, SG > 180 mg/dl)
 - MAGE
 - All these parameters daily, 2-hour postprandial and during night (10PM to 7AM)
 - Pump Compliance
 - Sensor Compliance, if necessary.

C.2.2 *Delivery information*

- Sensor and pump wear during delivery (yes/no)
- Patient satisfaction with treatment during delivery

C.2.3 *Neonatal outcomes*

- Mode of delivery (rates elective and emergency Caesarean Section, normal)
- Respiratory distress (1 and 5 minute Apgar scores)
- Gestational age at delivery, % preterm delivery < 37 weeks
- Infant birth weight (SD scores and customised birth weight percentile, % large for gestational age (LGA), % small for gestational age (SGA)
- Neonatal morbidity (treatment for neonatal hypoglycaemia)
- Neonatal care admission (duration of stay, level of care)
- Pregnancy related Serious Adverse Events (miscarriage < 22 weeks, congenital malformation, stillbirth, neonatal death)
- Feeding at hospital discharge (breast, bottle, both)

C.3 Study hypothesis

There is no hypothesis testing for this study. Analysis results will be presented by summary/descriptive statistics. Detailed statistical analysis plan will be described in the separate Biostatistical Plan (BP).

C.4 Study population

The study subject population is women with Type 1 Diabetes Mellitus at the age of 18-45 who

- plan pregnancy
- are in the early phase of pregnancy, up to the 16th week

C.5 Study design

A national prospective, multi-center, observational, Post-Market-Release study with CE marked and commercially available devices

C.6 Sample size

The minimum number of subjects to be enrolled is 100 women with complete follow-up of pregnancy from pre-conception until 6 weeks after delivery. Based on local data and experience, complete follow-up from the pre-conception phase will be possible for about 1/3 of the pregnancies. In about 2/3 of the cases, CSII will start during the first trimester of pregnancy, at the latest on the 16th week.

The expected total sample size is therefore 500 subjects including

- 100 subjects with complete follow-up – all phases on CSII, including SAP (pre-conception, pregnancy, 6 weeks after delivery).
- 300 subjects with pregnancy (enrollment up to the 16th week of pregnancy) and 6 weeks after delivery
- 100 subject with early termination (for various reasons like miscarriage, no conception within 12 months, etc.)

Enrollment will stop when data from 100 pregnancies with complete follow-up from pre-conception until 6 weeks after delivery have been collected.

C.7 Number of investigation sites and study duration

The Orchestra Foundation identified up to 30 sites in Poland to which they decided to make the pump donation (See the attached list, Annex L2.2).

The expected minimum number of subjects per investigation site is 2, the maximum number is 70. The numbers of subjects from the particular sites are based on the geography, potential, and level of experience of the site.

The time period for enrollment is 30 months, and started in May 2013. The treatment period is up to 22 months depending on in which phase of pregnancy the subject is enrolled. Data is collected at the beginning, during and at the end of the treatment period. Final report of the study is expected in 2018.

Table 1: Timelines of the study

| Project /Task | Start | End |
|---|----------------------------------|----------------------------------|
| Clinical study | Nov 2012 | Dec 2017 |
| <ul style="list-style-type: none"> • Kick-off • Enrollment • End of study | Nov 2012 May 2013 Feb 2017 | Nov 2012 Dec 2015 Dec 2017 |
| Data | May 2013 | Dec 2017 |
| <ul style="list-style-type: none"> • Data collection • • • Preliminary results • Data processing | May 2013 2017 Dec 2017 | Dec 2017 2017 Feb 2018 |
| Publication | Early 2018 | End 2018 |

D SUBJECT SELECTION

D.1 Inclusion criteria

A subject is eligible for the study if the following criteria are met:

1. Female diagnosed with Diabetes Mellitus Type 1
2. Subject indicated by HCP to start insulin pump therapy (CSII) or sensor augmented pump therapy (SAP) due to the desired or established pregnancy
3. HCP has prescribed the use of Orchestra donated device to the subject independently of the study
4. Signed Patient Informed Consent (PIC)
5. Subject is 18 to 45 years old, planning immediate pregnancy (within the next 12 months) or being pregnant within the first trimester until the 16th week of amenorrhea
6. Subject has been on MDI for at least 3 months before starting pump therapy

D.2 Exclusion criteria

A subject is excluded from the study if any of the following criteria are met:

1. Subject was enrolled in the registry earlier, and terminated it (for any reason)
2. Participation in any other interventional clinical trial – currently and/or in the last 3 months before the signature of PIC
3. Subject uses an insulin pump that was not donated by the Orchestra Foundation
4. Pregnant women with longer than 16 weeks of pregnancy/amenorrhea
5. Subjects who need assisted in vitro fertilization
6. Subjects with Diabetes Mellitus Type 2, Gestational Diabetes, MODY or any other type of diabetes than Type 1
7. Subject under the age of 18
8. Subject legally incompetent

9. Subject cannot read or write

E STUDY PREPARATION PROCEDURES

E.1 Investigator/Investigation site selection

The role of the principal investigator is to implement and manage the day-to-day conduct of the clinical study as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical study.

The Orchestra Foundation identified up to 30 sites in Poland to which they decided to make the pump donation (See the attached list, Annex L.2.2). Eligibility of the selected sites will be checked by HTA Consulting (CRO) as well as Medtronic monitors during the site initiation.

E.1.1 Clinical Investigation Agreement

A Clinical Investigation Agreement shall be in place, signed by the participating investigation site and/or principal investigator of each investigation site, as per the local legal requirements, and returned to Medtronic prior to the commencement of any clinical study activities. The investigator is indicating approval of the Clinical Investigation Plan and subsequent amendments, by a fully executed agreement. Amendments to this Clinical Investigation Plan shall be agreed upon between Medtronic and investigator(s) and be recorded with a justification for the amendments.

E.2 Ethics

E.2.1 EC/IRB approval

MEC approval is necessary for the publication of the study data in medical journals.

E.2.2 Informed consent process

Although a Patient Informed Consent (PIC) is not required for this study by Polish law and internal requirement, we have decided to implement an informed consent process with each study participant prior to start data collection. The PIC explains to the patient that the device(s) used in the study were donated by the Orchestra Foundation, and clearly states to whom and when to return the device(s) at study termination. The investigator or authorized designee must obtain written informed consent prior to subjecting the study participant to any study related activity.

During the consent discussion the investigator or his/her designee must fully inform the subject of the study in a non-technical wording understandable for the subject.

The subject must have ample time and opportunity to inquire about details of the study, and to decide whether or not to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the PIC form must be signed and personally dated by the subject and the investigator.

After all persons have signed and dated the PIC form the investigator must provide the subject with a copy of the signed and dated PIC form.

Any Medtronic monitor present (supporting the study) must review the signed PIC form prior to collecting any information from the subject.

E.2.3 Revisions in Patient Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the study. The investigator or his/her authorized designee should inform the subject in a timely manner.

Medtronic will revise the written Patient Information and Informed Consent Form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. In this case, the informed consent process has to be repeated, and the study subject has to sign and date the revised Patient Informed Consent Form.

E.2.4 Regulatory notification / approval

As all devices used in this study are CE marked, no additional regulatory requirements are applicable.

E.3 Regulatory compliance

This study will be conducted in compliance with the Declaration of Helsinki of 2008, laws and regulations of Poland in which the study is conducted, including data protection laws, the Clinical Investigation Plan, and clinical investigation agreement.

The principles of the Declaration of Helsinki have all been implemented in this study by means of the patient informed consent process, MEC approval, study training, clinical trial registration, risk benefit assessment, publication policy, etc.

E.4 Training requirements

Prior to investigation site activation or subsequent involvement in study activities, HTA Consulting (CRO) and Medtronic monitors will provide study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities. The investigation site team will be trained on the study related procedures including the Clinical Investigation Plan, the Patient Informed Consent process, the data collection tools, and electronic data collection systems during the initiation visit, and training will be documented in the clinical project file (sponsor file) and investigator site file.

Performed training will be documented prior to investigation site activation.

E.5 Study materials and study-specific equipment

An Investigator Site File is provided to each initiated investigation site.

E.6 Study device/product traceability

Medtronic is responsible for the manufacturing, packaging, labelling and distribution of all study devices, all devices used in this study are CE marked and commercially available in Poland. They will be stored and used according to their IFU.

Devices have been purchased by the Orchestra Foundation and are delivered to the hospitals that are responsible for storage, handling and disbursement of the devices to each study participant.

Patients should receive supplies to the study devices (sensors for the SAP group) at each scheduled visit. The insulin pump and the MiniLink transmitter provided to each subject are identified by various numbering sequences (i.e. serial numbers, lot numbers, manufacturer numbers, etc.). The serial number (SN) should be recorded on a per subject basis in the Device Tracking Log.

Except for Enlite sensors which are given free of charge, all the devices are loaned to the study participants for the study period, and will be returned to investigation site, and will be used by another eligible subject.

Consumables required to pursue insulin pump therapy will be prescribed (infusions sets) or purchased (reservoirs) by the patients according to routine practice during pregnancy in Poland. Insulin pumps and infusion sets are reimbursed for patients up to the age of 26. Infusion sets are reimbursed during pregnancy, over the age of 26 too. Reservoirs and CGM (sensors and MiniLinks) are not reimbursed for any group of patients.

Devices to be used in the study were purchased by the Orchestra Foundation and donated to the hospitals that will decide how to use them when the study is completed. Medtronic will not collect any devices at the end of the study.

F STUDY METHODS

F.1 Point of enrollment

The investigator will check beforehand if the patient would meet the inclusion and exclusion criteria, and then ask the patient, if she agrees to participate in the study. After signing and dating the PIC, the patient is considered enrolled in the study. When the investigator creates a new eCRF patient account, the system automatically generates a patient ID code. The patients' ID codes will be documented in the enrollment log.

F.2 Implant or procedure aspects

Procedures:

Patient enrolled before planned pregnancy

Visit 1a

- Inform the patient about study goals and procedures
- Ask the patient to sign and date the Patient Informed Consent form
- Ask patient to complete the HFS and DTSQs questionnaires
- Create a patient account in eCRF, and document the patient's ID code in the enrollment log
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the eCRF
- Check if the patient is properly trained on the loaned devices like the insulin pump, BG meter and sensor (if applicable)
- Document basal rate setting on the insulin pump
- Check the Bolus Wizard setting like the carbohydrate ratio, insulin sensitivity, target range, and active insulin time (if applicable)
- Check if the patient uses the reservoir and the infusion set as required
- If the patient is treated with SAP or she wants to use the sensor during the study period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the pump, how to insert the sensor, and how to use the MiniLink transmitter
- Check if patient is aware of product support, and if necessary, give her the product helpline telephone number
- Fill in the eCRF and submit the data
- Create a CareLink Clinical account, and upload the data from the insulin pump (and BG meter, if applicable)

If the patient is not properly trained, retraining is required. Then follow these training guidelines:

Patient training guidelines

Patients have to be properly trained on how to use the insulin pump and the consumables. Training is provided by the Health Care Professional (HCP) from the investigation site, or a Certified Product Trainer (CPT) based on the local practice. The trainer follows the standard training checklist during the training. When the training is completed, the checklist has to be signed by the patient and the trainer, and filed in the investigation site file.

Patients who are selected for insulin pump therapy only (without the sensor), receive the Paradigm REAL-Time 722 insulin pump. They are trained for the use of the insulin pump, and they do not have to be instructed on the CGM related features of the insulin pump, unless they intend to purchase and use sensors during the study period.

Patients who are selected for SAP (insulin pump and sensor), receive the Paradigm Veo 754 insulin pump. They have to be trained for all features of the insulin pump including the continuous glucose monitoring (CGM) features.

Product support, helpline

Patients have to be trained on how to do basic troubleshooting, and they have to receive the Product Support (Helpline) phone number from the trainer. In case of device related problems, they should contact the Helpline.

Sponsor representatives may perform study activities such as providing technical support and programming support during follow up.

Back-up therapy

In case of device failure, the patient should be able to switch to back-up therapy until replacement device is provided. It is recommended to keep syringes, insulin pens and insulin cartridges on hand as back-up.

Pump start, pump settings

Guidelines on how to start a patient on the insulin pump will be provided to investigation sites, and this document will be kept separately from the CIP.

Visit 2a – visit during pregnancy: 12th week (± 4 weeks window)

- Weigh the patient
- Measure the patient's blood pressure
- SAP treatment: If the patient has not used the sensor during the preconception period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the Paradigm Veo insulin pump, how to insert the sensor, and how to use the MiniLink transmitter
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 2b – no conception in 12 months (± 2 weeks window)

- Ask patient to complete the HFS and DSTQs questionnaires
- Weigh the patient
- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Visit 3 – visit during pregnancy: 24th week (± 2 weeks window)

- Ask patient to complete the HFS, DSTQs and DSTQc questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 4 – visit during pregnancy: 36th week (± 2 weeks window)

- Ask patient to complete the HFS and DSTQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 5 – optional visit after delivery (+ 2 weeks window)

- Weigh the patient before and after delivery
- Collect the delivery data listed in the relevant eCRF
- Collect the neonatal outcome data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 6 – 6 weeks after delivery (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Miscarriage – any time

- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data

- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Early dropout – any time

- Ask patient to complete the HFS and DTSQs questionnaires, if patient agrees
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Patient enrolled during pregnancy, up to the 16th week**Visit 1b (up to 16th week of pregnancy)**

- Inform the patient about study goals and procedures
- Ask the patient to sign and date the Patient Informed Consent form
- Ask patient to complete the HFS and DTSQs questionnaires
- Create a patient account in eCRF, and document the patient's ID code in the enrollment log
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the eCRF
- Check if the patient is properly trained on the loaned devices like the insulin pump, BG meter and sensor (if applicable)
- Document basal rate setting on the insulin pump
- Check the Bolus Wizard setting like the carbohydrate ratio, insulin sensitivity, target range, and active insulin time (if applicable)
- Check if the patient uses the reservoir and the infusion set as required
- If the patient is treated with SAP or she wants to use the sensor during the study period, make sure the patient is instructed on how to use the Continuous Glucose Monitoring feature of the pump, how to insert the sensor, and how to use the MiniLink transmitter
- Check if the patient is aware of product support, if necessary, give her the product helpline telephone number
- Fill in the eCRF and submit the data
- Create a CareLink Clinical account, and upload the data from the insulin pump (and BG meter, if applicable)

If the patient is not properly trained, retraining is required. Then follow these training guidelines:

Patient training guidelines

Patients have to be properly trained on how to use the insulin pump and the consumables. Training is provided by the Health Care Professional (HCP) from the investigation site, or a Certified Product Trainer (CPT) based on the local practice. The trainer follows the standard training checklist during the training. When the training is completed, the checklist has to be signed by the patient and the trainer, and filed in the investigation site file.

Patients who are selected for insulin pump therapy only (without the sensor), receive the Paradigm REAL-Time 722 insulin pump. They are trained for the use of the insulin pump, and they do not have to be instructed on the CGM related features of the insulin pump, unless they intend to purchase and use sensors during the study period.

Patients who are selected for SAP (insulin pump and sensor), receive the Paradigm Veo 754 insulin pump. They have to be trained for all features of the insulin pump including the continuous glucose monitoring (CGM) features.

Product support, helpline

Patients have to be trained for how to do basic troubleshooting, and they have to receive the Product Support (Helpline) phone number from the trainer. In case of device related problems, they should contact the Helpline.

Sponsor representatives may perform study activities such as providing technical support and programming support during follow up.

Back-up therapy

In case of device failure, patient should be able to switch to back-up therapy until replacement device is provided. It is recommended to keep syringes, insulin pens and insulin cartridges on hand as back-up.

Pump start, pump settings

Guidelines on how to start a patient on the insulin pump will be provided to investigation sites, and this document will be kept separately from the CIP.

Visit 3 – visit during pregnancy: 24th week (± 2 weeks window)

- Ask patient to complete the HFS, DTSQs and DTSQc questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 4 – visit during pregnancy: 36th week (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Make therapy adjustment, and change pump settings, if necessary
- Check infusion site, make sure patient uses infusion sets properly
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 5 – optional visit after delivery (+ 2 weeks window)

- Weigh the patient before and after delivery
- Collect the delivery data listed in the relevant eCRF
- Collect the neonatal outcome data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Visit 6 – 6 weeks after delivery (± 2 weeks window)

- Ask patient to complete the HFS and DTSQs questionnaires
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)
- Terminate pump therapy

Miscarriage – any time

- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)

Early dropout – any time

- Ask patient to complete the HFS and DTSQs questionnaires, if patient agrees
- Weigh the patient
- Measure the patient's blood pressure
- Collect the patient's medical data listed in the relevant eCRF
- Discuss with patient if she wants to continue the same therapy (CSII or SAP)
- Check infusion site, make sure patient uses infusion sets properly (if applicable)
- Make therapy adjustment, and change pump settings, if necessary
- Fill in the eCRF and submit the data
- Upload data into CareLink Clinical from the insulin pump (and BG meter, if applicable)



F.3 Data collection requirements

The time points at which data is collected are summarized in the **Table 2**

| Table 2 : Procedures and Data Collection at each visit | | | | | | | | | |
|---|-------------------------|-----------------------|-------------------------|---------------------|-------------------------|-------------------------|----------------|------------------------|---|
| Visit number | Visit 1 - Preconception | Visit 2a * | Visit 2b ** | Visit 1 - Pregnancy | Visit 3 | Visit 4 | Visit 5 *** | Visit 6 | Premature end of study |
| Visit type | Physical visit | Physical visit | Physical visit | Physical visit | Physical visit | Physical visit | Physical visit | Physical visit | Physical visit |
| Target study visit | Preconception planning | 12 weeks ammenorrhoea | 12 months | Pregnancy | 24 weeks of amenorrhoea | 36 weeks of amenorrhoea | Delivery | 6 weeks after delivery | At any time point (e.g. miscarriage, early dropout) |
| Tolerance window for the visit | | (± 4 weeks) | (± 2 weeks) | | (± 2 weeks) | (± 2 weeks) | (+ 2 weeks) | (± 2weeks) | |
| Procedures | | | | | | | | | |
| Patient Informed Consent | X | | | X | | | | | |
| Inclusion/exclusion criteria | X | | | X | | | | | |
| Assign Patient ID number | X | | | X | | | | | |
| Ask patient to complete HFS questionnaire | X | | X | X | X | X | | X | |
| Ask patient to complete DTSQs | X | | X | X | X | X | | X | |
| Ask patient to complete DTSQc | | | | | X | | | | |
| Complete eCRF - demographic and clinical characteristics | X | | | X | | | | | |
| Create Carelink Clinical account | X | | | X | | | | | |
| Upload data from insulin pump into CareLink Clinical | | X | X | | X | X | X | X | |
| Upload compatible BG meter into CareLink Clinical | | X | X | | X | X | X | X | |
| Check if patient is properly trained on Devices | X | | | X | | | | | |
| Record distributed devices in CRF and device tracking log | X | | | X | | | | | |
| Distribute supplies | X | X | | X | X | X | X | | |
| Complete follow-up eCRF | | X | x | | X | X | X | X | |
| Collect Serious Adverse Events | | X | X | | X | X | X | X | X |
| End of study eCRF | | | in case of no pregnancy | | | | | | X |
| Return of devices | | | in case of no pregnancy | | | | | X | X (early dropout) |
| * If patient is already pregnant at the time of enrollment, follow pcedures under 'Visit 1 - Pregnancy' | | | | | | | | | |
| ** Visit 2b is not applicable for women who became pregnant within 6 months of follow-up | | | | | | | | | |
| *** Data collection in eCRF in two weeks or during 'Visit 6' | | | | | | | | | |

The data to be collected in the eCRF at each visit is listed in the tables below.

Insulin and Continuous Glucose Sensor and blood glucose data are gathered automatically from the study pump and blood glucose meter which are uploaded at each visit into the CareLink Clinical account.

Data collection in the pre-conception period:

The first data collection and recording in eCRF takes place after the subject's enrollment.

| Data to be collected | |
|---|--|
| Diabetes type | |
| Diabetes duration | |
| Age | |
| White class | |
| Prior Insulin Regimen | |
| Basal insulin brand | |
| Daily basal insulin doses | |
| Bolus insulin brand | |
| Daily bolus insulin frequency | |
| Daily bolus insulin doses | |
| Total daily doses | |
| Pump model | |
| Serial number | |
| Insulin brand | |
| MiniLink serial number (if applicable) | |
| HbA1c - before conception, last value before insulin pump therapy started | |
| Weight | |
| Height | |
| BMI – to be generated by the algorithm | |
| Blood pressure | |
| Systolic | |
| Diastolic | |
| Hypoglycaemia history | |
| Number of severe hypoglycaemia over last the 12 months (per definition under F 5.1) | |
| DKA history | |
| Number of DKA over the last 12 months (per definition under F 5.1) | |

| | |
|--|----------|
| Microalbumin | |
| Albumin/creatinin | |
| Folic acid | |
| Diabetes complications | |
| Retinopathy | |
| Laser therapy | |
| Nephropathy | |
| Neuropathy | |
| Macroangiopathy | |
| Pregnancy history | |
| Number of successful pregnancies | |
| Number of pregnancies before | |
| Other medical conditions | |
| Other medications | |
| Medication description | |
| Any hospital admission of the last 12 months | |
| Number of SMBG per day | CareLink |

If conception does not occur within 12 months (from study start), the patient terminates the study. At this point, another data collection and recording in eCRF is required.

| | |
|-------------------------------|----------|
| Data to be collected | |
| Daily basal insulin doses | CareLink |
| Daily bolus insulin frequency | CareLink |
| Daily bolus insulin doses | CareLink |
| Total daily doses | CareLink |
| Daily basal doses | CareLink |
| Daily bolus doses | CareLink |
| Daily bolus | CareLink |
| HbA1c | |
| Weight | |
| Number of SMBG per day | CareLink |
| Severe Adverse Events | |

| | |
|--|--------------------------------|
| Severe Adverse Events related to devices | |
| Insulin pump serial number change, if applicable | |
| End of data collection | Date, within the window or not |

Data collection in the pregnancy period

During the pregnancy period, data collection and recording in eCRF is requested once in three months, optimally:

- 12th week (+/- 4 weeks)
- 24th week (+/- 2 weeks)
- 36th week (+/- 2 weeks)
- Miscarriage at any time

If there are 2 or more visits in the time period defined by the windows, the study doctor should select the data closest to weeks 12, 24 or 36 for documentation in the relevant eCRF.

| Data to be collected | |
|--|----------|
| Daily basal doses | CareLink |
| Daily bolus doses | CareLink |
| Daily bolus | CareLink |
| Pump usage compliance | CareLink |
| If CGM used (mostly VEO pumpers) | CareLink |
| Start of CGM | |
| HbA1c | |
| Weight | |
| BMI – to be generated by the algorithm | |
| Blood pressure | |
| Systolic | |
| Diastolic | |
| Microalbumin | |
| Albumin/creatinin | |
| Folic acid | |
| Other medical conditions | |
| Medications | |
| Medication description | |
| Any hospital admission | |

| | |
|--|----------|
| Number of SMBG per day | CareLink |
| Glucometer brand | |
| Severe Adverse Events | |
| Severe Adverse Events related to devices | |
| Insulin pump serial number change, if applicable | |
| Foetal growth information if available | |
| Complications diagnosed via ultrasound | |
| Complications descriptions | |
| Miscarriage | |
| Weeks of miscarriage | |
| Reason for termination | |

For the patients who did not start insulin pump therapy before the conception, data collection starts during the 1st visit after conception (up to week 16).

| | |
|--|--|
| Data to be collected | |
| Diabetes type | |
| Diabetes duration | |
| Age | |
| White class | |
| Prior Insulin Regimen | |
| Basal insulin brand | |
| Daily basal insulin doses | |
| Bolus insulin brand | |
| Daily bolus insulin frequency | |
| Daily bolus insulin doses | |
| Total daily doses | |
| Insulin pump model | |
| Insulin pump serial number | |
| MiniLink serial number (if applicable) | |
| Insulin brand | |
| HbA1C - last value before insulin pump therapy started | |
| Weight | |
| Height | |
| BMI – to be automatically generated by the algorithm | |

| | |
|--|----------|
| Blood pressure | |
| Systolic | |
| Diastolic | |
| Hypoglycaemia history | |
| Number of severe hypoglycaemia over the last 12 m (per definition under F 5.1) | |
| DKA history | |
| Number of DKA over the last 12 m (per definition under F 5.1) | |
| Microalbumin | |
| Albumin /creatinin | |
| Folic acid | |
| Diabetes complications | |
| Retinopathy | |
| Laser therapy | |
| Nephropathy | |
| Neuropathy | |
| Macroangiopathy | |
| Pregnancy history | |
| Number of successful pregnancies | |
| Number of pregnancies before | |
| Other medical conditions | |
| Other medications | |
| Medication description | |
| Any hospital admission of the last 12 months | |
| Number of SMBG per day | CareLink |

Further data collection and recording in eCRF is required once in every following 3 months during pregnancy, preferably on weeks 24 and 36.

| | |
|-----------------------------|----------|
| Data to be collected | |
| Daily basal doses | CareLink |
| Daily bolus doses | CareLink |
| Daily bolus | CareLink |
| Pump usage compliance | CareLink |
| Start of CGM | |

| | |
|--|----------|
| HbA1c | |
| Weight | |
| BMI | |
| Blood pressure | |
| Systolic | |
| Diastolic | |
| Microalbumin | |
| Albumin/creatinin | |
| Folic acid | |
| Other medical conditions | |
| Medications | |
| Medication description | |
| Any hospital admission | |
| Number of SMBG per day | CareLink |
| Glucometer brand | |
| Severe Adverse Events | |
| Severe Adverse Events related to devices | |
| Insulin pump serial number change, if applicable | |
| Foetal growth information if available | |
| Complications diagnosed via ultrasound | |
| Complications descriptions | |
| Miscarriage | |
| Weeks of miscarriage | |
| Reason for termination | |
| End of data collection | |

Data collection and recording in eCRF is required after miscarriage (up to week 22), stillbirth (after week 22), or early dropout at any time of pregnancy.

Data collection during delivery

Data collection is required during and after delivery. This data is recorded in eCRF during a visit within 2 weeks or during the final visit at study end.

| | |
|-----------------------------|--|
| Data to be collected | |
| <u>Maternal data:</u> | |

| | |
|--|----------|
| Daily basal doses | CareLink |
| Daily bolus doses | CareLink |
| Daily bolus | CareLink |
| Pump usage compliance | CareLink |
| HbA1c | |
| Weight before delivery | |
| Weight after delivery | |
| Number of SMBG per day | CareLink |
| Glucometer brand | |
| Sever adverse events | |
| Severe Adverse Events related to devices | |
| Delivery | |
| Date and Time of delivery | |
| Weeks of pregnancy | |
| Mode of delivery (elective CC, emergency CC or normal) | |
| Sensor use | |
| Survey – delivery and sensor use (5 questions, 4 x Yes/No, 1 x rating) | |
| <u>Neonatal data:</u> | |
| Weight | |
| Length | |
| Sex | |
| Apgar test 1min | |
| Apgar test 5min | |
| Glucose level | |
| Jaundice | |
| Neonatal care admission | |
| Numbers of days in Neonatal care admission | |
| Level of care description | |
| Congenital malformation | |
| Congenital malformation description | |
| Neonatal death | |

| | |
|-------------------------------|--|
| Neonatal death age | |
| Still birth | |
| Feeding at hospital discharge | |
| Reason for study termination | |
| End of data collection | |

Data collection 6 weeks after delivery

Final data collection and recording in eCRF is required 6 weeks after delivery.

| Data to be collected | |
|---|--|
| Daily basal doses | CareLink |
| Daily bolus doses | CareLink |
| Daily bolus | CareLink |
| Pump usage compliance | CareLink |
| If CGM used (mostly VEO pumpers) | |
| HbA1c | |
| Weight | |
| BMI | |
| Blood pressure | |
| Systolic | |
| Diastolic | |
| Microalbumin | |
| Albumin /creatinin | |
| Number of SMBG per day | CareLink |
| Glucometer brand | |
| Severe Adverse Events | |
| Severe Adverse Events related to devices | |
| Survey – delivery versus sensor use (5 questions, 4 x Yes/No, 1 x rating) | Only applicable if it was not done during the visit after delivery |
| Neonatal care admission | |
| Numbers of days in Neonatal care admission | |
| Neonatal death | |

| | |
|------------------------|--|
| Neonatal death age | |
| End of data collection | |

F.4 Role of the sponsor's representatives

The representatives of the Sponsor – Medtronic Poland Sp. z o.o. – may perform study activities such as providing technical support and programming support during follow up. These activities are performed under supervision and responsibility of the investigator and will not bias the data integrity in any way.

F.5 Source documents

The investigator will clearly mark clinical records to indicate that the patient is enrolled in this clinical investigation.

The data collection CRF will be filled in by the HCP based on information from the patient and the medical records kept at site.

The monitor shall have access to source documents, as well as other information needed to ensure investigator compliance with the CIP and applicable rules and regulations, and to assess the progress of the clinical study.

F.6 Adverse events

F.6.1 Definitions

For the purposes of the clinical report, Medtronic will classify each adverse event according to ISO 14155:2011 definitions.

Where the definition indicates “device”, it refers to any device used in the study. This might be the device under investigation, or any market released component of the system

Adverse Event (AE): (ISO14155:2011 3.2)

Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in patients, users or other persons, whether or not related to the investigational medical device

Potential Adverse Events:

- Infusion set adhesive could cause a skin reaction
- Infusion set can deliver too little or too much insulin
- Risk of inflammations and/or bruising at injection site

The incident rate for the above is anticipated to be low.

For more thorough risk assessment see document RAD 1068 in the IB.

NOTE 1: This definition includes events related to the investigational medical device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

Adverse Device Effect (ADE): (ISO14155:2011 3.1)

Adverse event related to the use of an investigational medical device

NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device

Serious Adverse Event (SAE): (ISO 14155:2011 3.37)

Adverse event that

- a) led to death,
- b) led to serious deterioration in the health of the patient, that either resulted in
 - 1) a life-threatening illness or injury, or
 - 2) a permanent impairment of a body structure or a body function, or
 - 3) in-patient or prolonged hospitalization, or
 - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

Severe hypoglycemia and diabetic ketoacidosis will be treated as Severe Adverse Events in this study.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): (ISO 14155:2011 3.36)

Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event

Unanticipated Serious Adverse Device Effect (USADE): (ISO 14155:2011 3.42)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

Device deficiency: (ISO 14155:2011 3.15)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance.

Potential Device Deficiencies include:

- Infusion set and the Enlite sensor can fall of
- Infusion set can be more or less effective in delivering insulin compared to standard products
- Infusion set and the Enlite sensor can break

NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Additional Definitions: Hypoglycemia and Hyperglycemia Events

Since it is inherent in the disease of diabetes that patients may daily experience variations in their blood sugar levels above and below the normal range, hypoglycemic or hyperglycemic events should not be defined and reported as an adverse event. Only severe hypoglycemic events or diabetic ketoacidosis (DKA)/Severe Hyperglycemia are to be treated as Adverse Events.

“**Severe Hypoglycemia**” is an event requiring assistance from another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that

the event was induced by a low plasma glucose concentration. **(American Diabetes Association Workgroup on Hypoglycemia, Diabetes Care 28:1245-1249, 2005)**

“**Severe Hyperglycemia**” is defined as Hyperglycemia (blood glucose >300 mg/dL) with blood glucose ketones >0.6mmol/L or accompanied by symptoms of nausea, vomiting or abdominal pain.

“**Diabetic Ketoacidosis/DKA**” is defined as: Hyperglycemia (blood glucose >250 mg/dL or <13.9 mmol/L) with either low serum bicarbonate (<15 mEq/L) and/or low pH (≤7.24) Anion gap (> 12) and either ketonemia or ketonuria and requiring treatment within a health-care facility. **(American Diabetes Association-Diabetes Care, Volume 27, Supplement 1, January 2004)**

Anticipated adverse events include severe hypoglycaemia, severe hyperglycemia, DKA, miscarriage, hospitalization because of uterine bleeding, and hospitalization because of instable glycemia.

F.6.2 Recording and reporting of Serious Adverse Events

The following Adverse Events need to be reported to Medtronic in the eCRF, as part of the study outcomes.

All serious adverse events and serious adverse device effects.

If applicable, these events need to be reported according to the table below:

Table 3

| Adverse Event reporting requirements | |
|--|---|
| Serious Adverse Events (SAE), Serious Adverse Device Effects (SADE) | |
| Investigator submit to: | |
| Medtronic | Immediately after the investigator first learns of the event. |
| Sponsor submit to: | |
| Regulatory Authorities | Reporting per cumulative SAE Report Table, immediately but not later than 7 calendar days following the date of awareness by the sponsor of the new event or update. A SAE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/patients, users or other persons, or a new finding to it: immediately, but not later than 2 calendar days after awareness by sponsor. |

All Adverse Events and Device Deficiencies will be reviewed by the Study Manager. This review will include the determination whether the Adverse Event/Device Deficiency meets regulatory reporting requirements. The sponsor will ensure timely Adverse Event/Device Deficiency reporting to meet global regulatory requirements.

Serious Adverse Event (SAE) and Serious Adverse Device Effect (SADE) information will be collected throughout the study and reported immediately to Medtronic Poland Spółka z ograniczoną odpowiedzialnością, ul. Ostrobramska 101, 04-041 Warszawa, Poland, tel.: **(+48 12) 421-88-32, (+48 12) 421-88-33** via an SAE/SADE Form incorporated in the eCRF.

Information reported on the SAE/SADE Form shall include a description of the event, the date of event onset, the relatedness of the event to the device, actions taken as a result of the event, length of hospital stay in number of nights, the outcome of the event, and the date the event was first noticed by the investigator.

F.6.3 Post Market Surveillance

F.6.3.1 Definition/classification

Product Complaint:

Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

F.6.3.2 Reporting of product complaints

All devices used in this study are market released. Therefore, Post Market Surveillance is applicable.

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for CE marked products.

Medtronic will notify the Competent Authority of the following incidents immediately on learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.

A serious deterioration in the state of health includes:

- Life-threatening illness or injury
- Permanent impairment of a body function or permanent damage to a body structure
- A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

F.7 Subject accountability

In accordance with the Declaration of Helsinki of 2008 and other applicable regulations, a patient has the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution. Patients may be removed from the study if any of the following events occur:

- Decision by the investigator or the sponsor that termination is in the patient's best medical interest
- Study discontinuation
- If a patient treated does not get pregnant within the 12 months of pre-conception phase, she terminates the study. She may keep the loaned devices for another 3 months unless it is needed for another patient. Data are not reported in eCRF, neither uploaded into CareLink Clinical for this period of time.
- If she stops using CSII for longer than 14 consecutive days during the study period
- If she stops coming to the follow-up visits (lost to follow-up)

If a patient is withdrawn from the study, the reason for withdrawal shall be recorded in the eCRF and in the patient's hospital record. If discontinuation is because of safety or lack of effectiveness, the patient shall be asked to be followed for collecting safety data.

Withdrawn subjects will be replaced until the number of 100 patients with full follow-up (pre-conception, conception, pregnancy, delivery, 6 weeks of lactation) is reached.

F.8 Study deviations and CIP changes

A study deviation is an event where the investigator or site personnel did not conduct the study according to the Clinical Investigational Plan, protocol, or Clinical Investigation Agreement. The investigator is not allowed to deviate from the above mentioned documents except with prior approval and under emergency circumstances. All deviations shall be documented and explained, regardless the reason for the deviation.

Medtronic retains the right to require the withdrawal of investigator / Investigational Site that violates the protocol.

The following deviations may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study.

Examples (the list of examples is intended as a guide and is not all-inclusive):

- Failure to obtain informed consent, i.e., there is no documentation of informed consent
- Enrollment of a subject who did not meet all inclusion/exclusion criteria
- Failure to report serious adverse event to sponsor
- Device dispensing error (i.e., use of an investigational device on a non-study subject)

If monitoring and/or auditing identify serious and/or persistent non-compliance on the part of an Investigator/Investigational Center, the Sponsor should terminate the Investigator/institution's participation in the trial.

The Investigator shall notify Medtronic within 5 days of the following deviations:

- A deviation to protect the life or physical well-being of a subject in an emergency
- Failure to obtain informed consent or use the appropriate informed consent form
- Enrollment of a subject not meeting the eligibility criteria
- Inappropriate use of the study device (i.e., use of an investigational device on a non-study subject)

No preapproval of any deviations will be granted. If deviations occur they must be reported.

Medtronic will assess the significance of all deviations and evaluate the need to amend the Clinical Investigation Plan or to early terminate the investigation, in accordance with Medtronic internal SOPs.

F.8.1 Request for approval of study deviations

The investigator shall obtain documented approval from Medtronic, before implementation, for any change in or deviation from the Clinical Investigation Plan. The investigator shall timely contact the Clinical Research Specialist or designee for review of the proposed change/deviation.

Prior approval is not always realistic in situations where unforeseen circumstances are beyond the investigator's control. However, also in these cases the event is considered a deviation, and shall be reported.

In any emergency situation the investigator shall exercise his/her judgment to safeguard the subject's interest. Such deviations from the Clinical Investigation Plan do not require the prior approval of Medtronic. The investigator shall report the deviation as soon as possible to Medtronic.

F.8.2 Reporting requirements for study deviations

The investigator shall adhere to EC/IRB requirements and procedures for reporting study deviations.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, additional training, terminate the study, etc.). Repetitive or serious investigator compliance issues may result in the need to initiate a corrective action plan, and in some cases freeze enrollment or ultimately terminate the investigator's participation in the clinical study. Medtronic will provide investigation site-specific reports to the investigators on a periodic basis summarizing information on deviations that occurred at the investigational site.

F.8.3 Amendments to the Clinical Investigation Plan

The investigator will propose any appropriate modification(s) of the Clinical Investigation Plan or investigational device or investigational device use. Medtronic will review this proposal and decide whether the modification(s) will be implemented.

G QUALITY CONTROL PROCEDURES

G.1 Procedures for database management

G.1.1 Data collection

An Investigator Site File (ISF) will be handed-out upon initiation.

The investigator must ensure accuracy, completeness and timeliness of the data reported in the CRFs and in all other required reports. Data reported on the CRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the patient file.

Only authorized persons can complete CRFs as specified on the DTL. CRFs shall be signed and dated by investigators (physician) as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in CRFs. If a person only authorized to complete CRFs makes changes to an already signed CRF, the investigator shall re-sign this CRF.

The pump data will be uploaded into CareLink Clinical.

A printed copy of the eCRF Forms to be used in this study will be kept separately of the CIP. In case EDC system would fail, paper copies of the eCRF forms can be made in order to be able to continue collection of study data.

All data is recorded in the medical records, and entered to the eCRF at data collection points.

G.1.2 Time windows for completion and submission of Case Report Forms

The investigator must ensure accuracy, completeness, legibility and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the investigator.

The eCRF shall be completed no later than three (3) weeks after patient visit and signed and submitted not later than four (4) weeks after patient visit.

SAE and SADE data must be reported immediately.

G.1.3 Data review and processing

Data management will be done according to Medtronic internal SOPs. These documents will be made available on request.

A minimum of 25% of total patient data Case Report Forms (CRFs), calculated from the total number of separate case report forms determined to be source verifiable and received in the database, will be source verified before database freeze for the final report without possibility on verification by person from Medtronic.

Priority of source data review should be given to the following electronic Case Report Forms: Baseline Data (demographic data, glycemic control, HbA1c), first follow-up during pregnancy week 12 – glycemic control, HbA1c), last follow-up during pregnancy (week 36 – glycemic control, HbA1c), 6-week follow-up during lactation phase (neonatal data, neonatal care admissions). The 6-week visit in lactation phase would include any preterm delivery CRFs that have been completed. In addition, all procedure related Adverse Events will be monitored 50% and applicable copies of source data will be sent to the Clinical Safety Specialist. No patient identifiable data may appear on these copies.

Monitoring activities may include, but are not limited to, review of regulatory documents patient informed consent documentation. In addition, any applicable local laws and regulations will be followed. Control visits will be documented via a Monitoring Visit Report. The monitoring report is reviewed by the Study Manager to ensure that the sites follow the protocol, and that all the regulatory requirements are fulfilled. The findings in the report will be translated into actions to resolve any issues observed. The Monitoring Visit Follow-up Letter will be sent to the Principal Investigator.

G.2 Monitoring procedures

Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Medtronic internal SOPs and the Monitoring Plan.

Site initiation of the study will be conducted by HTA Consulting. Medtronic monitors may take part in site initiation too. Site closure will be conducted by HTA Consulting and Medtronic monitors. Regular monitoring visits during the study will be conducted by the Medtronic monitors according to the Monitoring Plan that will be kept separately from this CIP.

G.2.1 Accessibility of investigation site staff and study materials

The principal investigator(s), his/her delegate(s) and the study coordinator(s) shall be accessible to Medtronic personnel involved in the study management and monitoring. This accessibility is of particular importance for reviewing data in the Case Report Form (CRF). Direct access to patient records for source data verification will need to be granted and prepared prior to any monitoring visits.

G.2.2 Audits and investigation site inspections

In addition to regular monitoring visits, Medtronic may conduct audits at participating investigation sites. The purpose of an audit is to verify the adequate performance of the study related activities. Independent of the employees involved in the study. Regulatory bodies may also perform inspections at participating investigation sites.

The investigator and/or institution shall permit Medtronic and regulatory bodies direct access to source data and documents, taking into account any restrictions due to local law, to perform study-related monitoring, audits, and regulatory inspections.

Any competent authority announcements shall be forwarded to the Study Manager. Investigation sites will be required to provide access to source documents and data to the bodies mentioned above.

G.3 Study suspension or early termination

G.3.1 Early study suspension or termination

Medtronic may decide to suspend or prematurely terminate the study (e.g. if information becomes available that the risk to study subject is higher than initially indicated, if interim analysis indicates that the results significantly differ from the study objectives or statistical endpoints, or because of a business decision). If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators of the termination or suspension and the reason(s) for this. Principal Investigators will also promptly inform the study participants about the termination or suspension of the study.

G.3.2 Early investigation site suspension or termination

Medtronic may decide to suspend or prematurely terminate an investigation site (e.g. in case of non-compliance to the Clinical Investigation Plan or lack of data collection requirements). If an investigation site is suspended or prematurely terminated, Medtronic shall promptly inform the clinical investigator(s) of the termination or suspension and the reason(s) for this. If proper correction is made, and suspension of the investigation site is lifted, Medtronic shall promptly inform the principal investigator(s) about the change and the reason(s) for the change. The principal investigator(s) will inform the study participants.

G.3.3 Subject follow-up in case of termination

In case of early termination of the study all patients already enrolled will be called into hospital for a closing visit. During this visit, it will be up to the investigator to decide whether the patient can keep using the loaned devices or not.

G.4 Study close out

After all patient follow-ups have been completed; the Medtronic monitors will visit each center. During this visit, the monitors will discuss and verify the following items for study closure:

- Remaining action items closure
- Final study payments
- Investigator Agreement termination
- Archiving and storage of study documents, in adequate space.

At the study site, study documents and all source documents must be retained at least 20 years after study closure.

When all CIP requirements have been met or if for any reason the study is terminated, a letter describing the status of the final study responsibilities will be provided to principal investigator.

H DATA ANALYSIS AND REPORTING

A Biostatistical Plan (BP) will be prepared and kept separately from the CIP.

H.1 Analysis of clinical data

H.1.1 Analysis of Primary Objectives

Descriptive analysis will be performed for all available groups: 1) all enrolled; 2) those who failed to achieve a pregnancy; 3) those who become pregnant after the pre-conception phase; 4) those who already pregnant and enrolled after.

Glycemic control measured by HbA1c

Calculate descriptive statistics for HbA1c

- A1C and change of A1c
 - from baseline
 - each Pregnancy trimester
- Proportion of subjects achieving A1C < 6% (6.5%, 7%, 7.5%, 8%)

Glycemic Control measured by Continuous Glucose Monitoring Data (for subjects with available sensor data (SG) only)

Calculate descriptive statistics for Sensor glucose distribution, the following variables will be analyzed as overall and stratified by pregnancy outcome (no conception, delivery, miscarriage, etc.) and completeness of treatment phase (complete follow-up, pregnancy and 6 weeks after delivery, pre-conception phase only, etc.)

- Mean SG per subject per day
- SG variation (CV, SD, MAGE) per subject per day
- % of SG < 50mg/dL, 50-60mg/dL, 60-70mg/dL, 70-120mg/dL, 120-140mg/dL, 140-180mg/dL, 180-250mg/dL and > 250mg/dL per subject per day
- AUC of SG < 50mg/dL, < 60mg/dL, < 70mg/dL, > 140mg/dL, >180mg/dL and > 250mg/dL

per

- Pregnancy trimester
- Duration of treatment received
- Sensor compliance (% of time sensor wear) in SAP group only

The analysis will be repeated for listed variables based on 2-hour postprandial CGM data and night only (10pm to 7am) data.

Glycemic Control measured by SMBG Data

Calculate descriptive statistics for SMBG distribution, the following variables will be analyzed as overall and stratified by pregnancy outcome (no conception, delivery, miscarriage, etc.) and completeness of treatment phase (complete follow-up, pregnancy and 6 weeks after delivery, pre-conception phase only, etc.)

- N, Mean, Median, SD, Min and Max per subject per day per
- Pregnancy trimester
- Duration of treatment received

H.1.2 Analysis of Secondary Objectives

Pregnancy Outcomes

Calculate incidence rates for the following events as overall and by duration of treatment received.

- Mode of Delivery
 - Normal
 - Elective CS
 - Emergency CS
- Preterm Delivery (< 37 weeks)
- Miscarriage (< 22 weeks or \geq 22 weeks)
- Neonatal Morbidity
 - Neonatal Hypoglycaemia
 - Other
- Other Pregnancy Related Serious Adverse Events

Neonatal Outcomes

Calculate descriptive statistics for the following as overall and by duration of treatment received.

- Respiratory Distress
 - 1 and 5 minute Apgar scores
- Infant Birth Weight
 - SD scores
 - Customised birth weight percentile (LGA, SGA)

Provide frequency tables for the following variables

- Neonatal Morbidity
 - Treatment for Neonatal Hypoglycaemia

- Neonatal Care Admission
 - Duration of Stay
 - Level of Care

- Feeding at Hospital Discharge
 - Breast
 - Bottle
 - Both

Questionnaire and Surveys

The questionnaire and survey results will be presents and by time of questionnaire/survey collected

- Hypoglycaemia Fear Survey (HFS)
- Diabetes Treatment Satisfaction Questionnaire
 - DTSQs
 - DTSQc

Other Maternal Outcomes

Calculate descriptive statistics for the following variables

- Weight
- BMI
- Daily Insulin Requirements (units) at the moment of the visit
- Microalbumin excretion with albumin/creatinine ratio
- Number of SMBG per subject per day (patient self-reported)

per

- Pregnancy trimester
- Duration of treatment received

Device Information at Delivery

Calculate the proportion of pump and/or sensor wear (yes/no) at time of delivery Summary survey results for patient satisfaction with treatment during delivery

Safety Analysis

All site reported adverse events for enrolled subjects will be summarized, including:

- Incidence of severe (clinical) hypoglycemia
- Incidence of DKA
- Serious adverse events (SAE)
- Unanticipated device effects (UADE)

Detailed information of all adverse events will be provided in listings. The summary of adverse events will also be provided per trimester.

Baseline Information and Demographic Characteristics

Baseline information and demographic characteristics such as age, gender, weight, BMI, diabetes duration, insulin regimen, etc. will be summarized. Medical information such as previous severe hypoglycemia and DKA history up to 12 month prior to study start will also be summarized.

Subject Disposition and Center Specific Information

Number of subject screened enrolled, withdrawal, complete of each pregnancy phase and study will be reported. The number of subjects assigned to CSII/SAP group, with or without sensor will also be provided as overall and for each center.

H.2 Publication Policy

A Publication Committee will be established.

Publications and presentations referring to the 'Pregnancy Observational Study in Poland' will be coordinated by the Publication Committee and Medtronic to allow the use of all available data.

All parties – the Publication Committee, Medtronic and the Orchestra Foundation – intend to publish the results of the registry in both international and local (Polish) medical journals.

The following publication policy will have to be adhered to by all participating investigation sites.

Authorship on any publication(s) resulting from this study will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the Vancouver principles (The Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, ICMJE, October 2008), as agreed upon by the editors of all major medical journals.

The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

A single investigation site may access and use the data provided by itself for scientific publications following prior approval by the Publication Committee and the Orchestra Foundation.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval from the Publication Committee and the Orchestra Foundation.

Medtronic can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use after the approval by the Orchestra Foundation.

The study sponsor will collect data in such way that no patient can be identified, and monitor study records.

Participating patients will not be identified by name in any published reports about the study.

I STUDY MANAGEMENT

I.1 Study staff

This study is sponsored by

Medtronic Poland Spółka z ograniczoną odpowiedzialnością

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04-041 Warszawa

Tel.: +48 - 22 4656900

Fax: +48 - 22 4656917

An independent company, HTA Consulting, will be performing some activities of the study as described in this CIP, under the supervision of Medtronic.

The list of study staff contact details is listed in Annex K2.1.

The sponsor will maintain the list and provide updates if needed.

I.2 Advisory committees

A Steering Committee of medical advisers and Medtronic representatives was established.

The roles and responsibilities of the Steering Committee are documented in the separate Steering Committee Charter

1.2.1 Publication Committee

A Publication Committee of medical advisers and Medtronic representatives will be installed. The roles and responsibilities of the Publication Committee will be described in a separate document.

I.3 Records and reports

1.3.1 Investigator records

The investigator must retain the Investigator Site File, patient data sources and CRFs in accordance with local law and regulations for 20 years.

The investigator should take measures to prevent accidental or early destruction of the study related materials.

1.3.2 Investigator reporting responsibilities

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, serious adverse events/serious adverse device effects, and any deviations from the Clinical Investigation Plan.

1.3.3 Sponsor records

At a minimum, the sponsor will keep the following records:

- All essential study documents and correspondence that pertains to the trial
- CIP and, if applicable, any amendments
- Delegated Task Lists and training records of investigators and site staff
- Signed Clinical Investigation Agreements and signed agreements with third parties
- Medtronic approved Patient Informed Consent Form
- Site initiation reports, regular monitoring visit reports, and monitoring visit reports for close out

- Adverse event and Device Deficiency reports
- Fully executed CRFs and corrections

Some of these documents may be kept by the CRO during the course of the study and will be handed to Medtronic after all study activities will be completed.

1.3.4 Sponsor reporting responsibilities

When the investigator records a SAE or SADE, HTA Consulting and the Study Manager will be promptly notified about the event by e-mail. The Study Manager must report all SADE to SBU within 48 hours. SBU will notify the local authorities, if necessary. Non-device related SAE, including but not limited to miscarriage, severe hypoglycaemia, diabetic ketoacidosis will not be reported outside, they will be recorded for the purpose of the study outcomes.

1.3.5 Record retention

The investigator must retain the Investigator Site File, patient data sources and CRFs in accordance with local law and regulations for 20 years after study closure.

The investigator should take measures to prevent accidental or early destruction of the study related materials.

1.4 Miscellaneous

1.4.1 Subject compensation and indemnification

Patients will not receive any compensation for participation in this study.

Medtronic shall pay, as compensation, investigators/Medical Centers, in full and exclusive compensation for the duties conducted and assignments. A separate clinical investigation agreement will be put into place with each participating center and/or investigator detailing this compensation. HTA Consulting will be responsible to manage the agreements directly with the sites.

1.4.2 Subject confidentiality

All records and other information about patients participating in this study will be treated as confidential.

Participating patients will not be identified by name in any published reports about the study.

J RISKS AND BENEFITS

J.1 Anticipated Clinical Benefits

Management of diabetes during pregnancy needs to ensure an appropriate A1c is attained before and during pregnancy while reducing the mothers' exposure to hypoglycaemia and severe hypoglycaemic events, and reducing the foetus' exposure to hyperglycaemia. Sensor-augmented pump therapy provides the technology to enable reductions of A1c, to anticipate and alert the mother to glucose levels outside the target range, and to assist in preventing severe-hypoglycaemic events without the risk of rebound hyperglycaemia.

J.2 Risks

All devices used in this study are released for distribution by Medtronic. Medtronic is not aware of any significant problems with this product. In the study, the products will be used in accordance with their labelling; therefore no risks other than the risks typically associated with a routine device use, and follow-ups are anticipated.

In addition patients are treated according to general clinical practice, so no extra tests and follow-ups are required. Therefore, no additional risks are associated with participation in this study.

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L APPENDICES

L.1 Names and addresses

L.1.1 List of contact persons

Coordinating clinical investigator

[REDACTED]
[REDACTED]
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Other contacts

Contract Research Organization:

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L.1.2 List of participating investigation sites and investigators

A Contacts List of investigation sites and principle investigators in a printed format will be kept separately from the CIP.

L.2 Case Report Forms

A sample eCRF in a printed format will be kept separately from the CIP.

L.3 Patient Questionnaires

The Hypoglycemia Fear Survey (HFS) and the Diabetes Treatment Satisfaction Questionnaire (DTSQs - status version, DTSQc - change version) will be provided in Polish to the patients.

L.4 Abbreviations

| | |
|----------------|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AUC | Area under The Curve |
| A1c/A1C | Glycated/Glycosylated Hemoglobin |
| BP | Biostatistical Plan |
| CGM | Continuous Glucose Monitoring |
| CS | Caesarean Section |
| CIP | Clinical Investigation Plan |
| CRO | Contract Research Organization |
| DMC | Data Monitoring Committee |
| DTL | Delegated Tasks List |
| DTSQ | Diabetes Treatment Satisfaction Questionnaire |
| e-CRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| FU | Follow up |
| HbA1c | Glycated/Glycosylated Hemoglobin |
| HFS | Hypoglycemia Fear Survey |
| HTA Consulting | – contracted CRO |
| ISF | Investigator Site File |
| MAGE | Mean Amplitude of Glucose Excursion |
| MDI | Multiple Daily Injections |
| MEC | Medical Ethical Committee |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SG | Sensor Glucose (glucose concentration measured by the sensor) |
| SOP | Standard Operating Procedure |

Intentionally left blank.

Change History record

| CIP Change History | | |
|--------------------------------|--|------------|
| Version | Summary of Changes | Author |
| Version 1.0 Initial release | Initial release A, D. 1 - Inclusion criteria: "Subject having a male partner" deleted 8. 2 - Use of preferred / accepted BG meters explained E. 5- Information on current reimbursement status of CSII and CGM in Poland added F. 2 - Patient questionnaires: DTSQ added, HFS t, melines adjusted G. 1. 3- Priority of source data review adjusted G. 2- Medtronic monitors' responsibility specified Wording and text adjustments | [Redacted] |
| Version 3.0 | A, Treatment - sensor use A, 8. 2 - device certificate references removed A., D. 1, D. 2 Inclusion/Exclusion criteria - wording adjustment, "Use of contraception during insulin pump therapy" deleted; Adjustment of endpoints A. Planning phase extended from 6 to 12 months C. 7 - Adjustment of study timelines F. 2, F. 3 - Extension of planning phase from 6 to 12 months F. 3 - 'Microalbumin/creatinin' replaced by 'Albumin/creatinin' F. 4- 'Role of sponsor representatives' added H. 1 - Detailed 'Analysis of clinical data' added H. 2 - 'Publication policy' adjusted I. 2 - 'Advisory committees' adjusted L. 1 - Names and addresses updated Wording adjustments based on new CIP template | [Redacted] |
| Version 4.0 | Author: new Study Manager A. CSII and SAP: replaced by "CSII including SAP" duration of enrolment period, "Sensor compliance" deleted SAP: replaced by "CSII including SAP" C. 3 New wording C. 7 Updated timelines H. 1 Adjusted wording | [Redacted] |