



Study Protocol RD002489

Version 1.0,  
AC Connect School Study

**ACCU-CHEK® CONNECT AT SCHOOL (CATS) PEDIATRIC STUDY**

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8 Aug 2015

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**Confidentiality Statement**

The information contained in this document, especially unpublished data is, the property of the Roche Diabetes Care, Inc. It is provided to you in confidence as an Investigator, potential Investigator, or consultant, for review by you, your staff or an Institutional Review Board (IRB). It is understood that this information will not be disclosed to others without written authorization from Roche Diabetes Care, Inc., except to the extent necessary to obtain informed consent from subjects who potentially will participate in the study.

## **SUMMARY OF REVISION HISTORY**

<b>Version</b>	<b>Date of issue</b>	<b>Reason for change</b>
1.0	25-Aug-2015	New version

**Coordinating Investigator:**

 MD MRCP MHA

**Responsibilities of the Coordinating Investigator:**

The Coordinating Investigator supports the Sponsor (Roche Diabetes Care, Inc.) with the design of the study, finalization of the study protocol and all relevant study training materials.






During the conduct of the clinical study, the Coordinating Investigator will provide scientific advice and support the Sponsor in writing study publications.

In addition, the Sponsor might request that the Coordinating Investigator coordinate the work in this study and support the submission process to the Institutional Review Board (IRB) and/or Regulatory Authorities.

The Sponsor shall maintain an updated list of Principal Investigators, study sites, and institutions. This list can be kept separately from the protocol and provided to Principal Investigators. The definitive list shall be provided with the clinical study report.

**Steering Committee**

The Steering Committee is composed of sponsor representatives and external consultants. The Committee will provide scientific and strategic directions for the trial and will have overall responsibility for the design, execution, and publication of the observational study. The Steering Committee will convene regularly during the trial (teleconferences or face-to-face meetings) to discuss and report on the study progress. External members include:

- , PhD, CDE
- , M.D. MRCP MHA, pediatric endocrinologist
- 
- , RN, CDE
- , RN, CDE, school staff



## SIGNATURE SHEET FOR INVESTIGATORS

Principal Investigator

City

Country

### Study Protocol RD002489

### ACCU-CHEK<sup>®</sup> CONNECT AT SCHOOL (CATS) PEDIATRIC STUDY

I have thoroughly read and reviewed the above study protocol, and I agree that it contains all necessary details for carrying out this study.

I agree to conduct the study as specified in this study protocol and in accordance with the principles of the Guidelines of the International Conference on Harmonisation (ICH) on Good Clinical Practice (GCP) where it can be applied to medical devices, with the Declaration of Helsinki, and FDA 21 CFR Parts 11, 50, 54, 56, 803, 812, 814 and 820.30; as applicable, with all local laws and regulations and with the regulatory requirements for source data verification.

I fully understand that any changes instituted by the Investigator(s) without previous discussion with the appropriate sponsor personnel would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I will discuss this material with subjects to ensure they are fully informed regarding the investigational device and the conduct of the study. I will use only the Informed Consent Form approved by the Sponsor and will fulfill all responsibilities for submitting pertinent information to the Institutional Review Board (IRB) responsible for this study.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Roche Diabetes Care, Inc.

I agree that the Study Monitor/Clinical Research Associate (CRA), and/or other Sponsor representatives shall have access to any source data from which case report form information may have been generated.

To be signed by the Principal Investigator and Sub- or Co-Investigator (as appropriate).

***Please sign and date next to your printed name:***

PRINTED NAME	Signature	Date (dd-mmm-yyyy)

If more space is needed, please use a second copy of this page.



## Protocol Outline

For comprehensive details, please refer to the respective sections.

Study Title:	ACCU-CHEK® CONNECT AT SCHOOL (CATS) PEDIATRIC STUDY
Short Name	AC Connect School Study
Investigational Devices:	ACCU-CHEK® Connect Diabetes Management System (DMS)
Comparative Devices:	The Control Group will continue to use their current diabetes management devices.
Working Hypothesis:	Use of ACCU-CHEK® Connect DMS over a period of 6 months will reduce diabetes-related distress in parents/caregivers of school-age children and adolescents with type 1 diabetes on multiple daily injections (MDI) therapy.
Primary Objective:	The primary objective of this study is to assess change in diabetes-related distress among parents/caregivers of school-age children on MDI therapy (PAID- C & T Parent Questionnaire) after 6 months utilization of the ACCU-CHEK® Connect DMS compared with usual care.
Secondary Objectives:	<p>The secondary objectives of this study are to assess the changes in the following measures after 3 and 6 months utilization of the ACCU-CHEK® Connect DMS compared with usual care:</p> <ul style="list-style-type: none"> <li>• Change in diabetes-related distress among parent/caregiver. (PAID C &amp; T Parent Questionnaires) at 3 months compared to Baseline</li> <li>• Change in diabetes-related distress among school-age children and adolescents with diabetes. (PAID-C &amp; T Child Questionnaires) at 3 and 6 months</li> <li>• Change in perceived family conflict among school-age children with diabetes and parent/caregiver. (DFCS-parent and DFCS-youth Questionnaire) at 3 and 6 months</li> <li>• Change in affect toward blood glucose monitoring (BGM) among school-age children with diabetes and parent/caregiver. (BGMC-parent and BGMC-youth Questionnaire) at 3 and 6 months</li> </ul> <p>changes in glycemic control: (HbA1c, Percentage in Glucose Target Range, Glycemic Variability, Hypoglycemia)</p> <p>Intervention Group Only at 6 Months:</p> <ul style="list-style-type: none"> <li>• Use of, Preference, Satisfaction with the ACCU-CHEK Connect DMS (All)</li> </ul>
Indication	Type 1 diabetes
Target Population	School-age children/adolescents with type 1 diabetes on MDI therapy and their parents/caregivers
Number of Subjects	Between 150 and 200 subjects
Number of Sites	8 to 13 Pediatric Endocrinology Practices
Study Design:	Prospective, interventional, multi-center, post-market, 6-months, cluster randomized study, conducted in the US,;
Study groups	<ul style="list-style-type: none"> <li>▪ Interventional Group: ACCU-CHEK® Connect Diabetes Management System</li> <li>▪ Control Group: Usual care: Continued use of subjects' current diabetes devices</li> </ul>
Study Duration:	6 months treatment phase

Inclusion Criteria	<p><u>Child/adolescent and 18 year old with diabetes</u></p> <ul style="list-style-type: none"> <li>• Diagnosis of type 1 diabetes for <math>\geq 3</math> months</li> <li>• Currently managed with multiple daily insulin injections (MDI);</li> <li>• 6-18 years of age inclusive at enrollment (Visit 1)</li> <li>• Attending full day school schedule (K-12 grades)</li> <li>• Able to provide SMBG data minimum of one month prior to study start</li> <li>• Currently using a Smartphone with ability to download the ACCU-CHEK Connect System App accordingly OR ability to use Smartphone provided for use in study</li> </ul> <p><u>Child/adolescent with Diabetes and Parent(s)/Caregiver(s):</u></p> <ul style="list-style-type: none"> <li>• Parents/Caregivers &amp; Adolescent (18 years) provide written informed consent</li> <li>• Child (7-17 years) with diabetes provide age appropriate child assent</li> <li>• Parent/caregiver currently using a Smartphone and able to receive SMS/MMS messages Able to read and write in English language</li> <li>• Willing and able to comply with study procedures</li> </ul>
Exclusion Criteria	<p><u>Child/adolescent with diabetes</u></p> <ul style="list-style-type: none"> <li>• CSII therapy or known planned MDI to CSII transition within the study period</li> <li>• CGM use during the course of the study (both home and/or professional CGM)</li> <li>• Remote data sharing system/device use during the course of the study (i.e. NightScout, DexCom Share, Medtronic Connect)</li> <li>• Pregnancy</li> <li>• Diagnosed with any clinically significant condition (e.g. major organ system disease, infections, psychosis or cognitive impairment);</li> <li>• Subject requires chronic steroid in adrenal suppressive doses, other immuno-modulatory medication or chemotherapy;</li> </ul> <p><u>Child/adolescent with diabetes and Parent(s)/Caregiver(s)</u></p> <ul style="list-style-type: none"> <li>• Visual impairment preventing the complete use of ACCU-CHEK<sup>®</sup> Connect system;</li> <li>• Parent/Caregiver is investigator or sub-investigator, general practitioner, practice staff, pharmacist, research assistant or other staff or relative of those directly involved in the conduct of the study and design of the protocol.</li> </ul>
Study Visits	<p>Visit 1 Baseline: Office Visit – Study Start</p> <p>Visit 2 (Week 1): Phone Call</p> <p>Visit 3 (Month 3): Office Visit</p> <p>Visit 4 (Month 6): Office Visit – Study End</p> <p>Visit 5 (2-5 days after V4) – only if ongoing Adverse Event at Visit 4</p>
Sample Size Calculation	<p>Change from baseline in PAID-C &amp; T parent: Powering at 80% power to detect a treatment effect of 0.460 with 75 patients per group and a significance level of 0.05. Given assumptions of SD of 5 to 16, the sample size would be able to detect treatment group differences of 2.3 (SD=5) to 7.4 (SD=16.0). 100 subjects per group will be enrolled to accommodate attrition.</p>
Statistical Methods	<p>The primary analysis method for the primary objective will be where the dependent variable will be the change from baseline to 6 months in the PAID, with treatment group as the independent variable, and baseline PAID, child demographic and diabetes history characteristics as covariates. ANCOVA methods will also be used to analyze the secondary variables. Descriptive statistics will be provided for all outcomes over time by treatment group. The usability, satisfaction and preference questions for the intervention group will</p>

	be summarized by question descriptively by the scale value of each question (mean, standard deviation, range, 95% CI), and the distribution of responses within the group (n and percent of subjects at each level of response).
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## Schedule of Assessments

	Visit 1 Baseline	Visit 2	Visit 3 Month 3	Visit 4 Month 6	Visit 5 -
	Day 1	Week 1 ± 2 days	Week 12 ± 2 weeks	Week 24 ± 2 weeks	2-5 d > V 4
	In Office	Phone Call	In Office	In Office	Phone Call
Informed consent/assent	X				
Check Eligibility and Smartphone compatibility	X				
Pregnancy test, if applicable	X				
Demographic data and other Baseline data	X				
Diabetes Background, Devices, History & Medications	X				
Record number of days diabetes related missed from Work (parent/caregiver) /school (child) in previous 3 months	X		X	X	
Collect height and weight	X		X	X	
HbA1c (Central Lab)	X		X	X	
Administer Questionnaires	X		X	X	
Record brand of current BG meter & serial number.	X				
Download SMBG data using existing site process	X		X <sup>2</sup>	X <sup>2</sup>	
Review and discuss SMBG data with patient/parents and agree on modification of SMBG regimen, if needed.	X		X <sup>1 2</sup>	X <sup>1 2</sup>	
Download current BG meter data using Diasend for eCRF	X		X <sup>2</sup>	X <sup>2</sup>	
Dispense to interventional group					
• ACCU-CHEK <sup>®</sup> Connect DMS devices	X <sup>3</sup>				
o Record BG meter serial number(s)	X <sup>3</sup>				
• ACCU-CHEK <sup>®</sup> Call Center Cards	X <sup>3</sup>				
• Smartphone, if applicable	X <sup>3</sup>				
Perform Training and Set up ACCU-CHEK <sup>®</sup> Connect DMS (connectivity, portals and invitations)	X <sup>3</sup>				
Record Malfunction of /complaints about any device, if any	X	X	X	X	
Record AE / SAE, if any	X	X	X	X	
Schedule new appointment(s)	X		X		
Follow-up call 2-5 days after Last Visit (only if ongoing AE(s))					X
Update electronic CRF	X	X	X	X	X

<sup>1</sup> Intervention group review data captured in ACCU-CHEK Connect DMS

<sup>2</sup> Control Group review usual care SMBG data with current diabetes management devices

<sup>3</sup> Intervention group only

## Abbreviations

AC® Connect DMS	ACCU-CHEK® Connect Diabetes Management System
AE	Adverse Event(s)
BGM	Blood Glucose Monitoring
BGMC	Blood Glucose Monitoring Communication
C	Child
CFR	Code of Federal Regulations
CGM	Continuous Glucose Monitoring
CI	Confidence Interval
CIP	Clinical Investigation Plan; synonym for protocol
CRA	Clinical Research Associate
CSII	Continuous Subcutaneous Insulin Infusion
CSR	Clinical Study Report
DFCS	Diabetes Family Conflict Scale
DKA	Diabetic Ketoacidosis
DMS	Diabetes Management System
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCP	Healthcare Professional
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB	Institutional Review Board
ISO	International Organization for Standardization
ITT	Intent-to-Treat (population)
MedDRA	Medical Dictionary for Regulatory Activities
MDI	Multiple Daily Injections
PAID	Problem Areas in Diabetes (PRO) in various versions: PR, T and C
PP	Per Protocol
PRO	Patient Related Outcome
Protocol	Synonym for CIP
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SDV	Source Data Verification
T	Teen
T1DM	Type 1 Diabetes Mellitus
V	Visit

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# 1 Introduction

## 1.1 Introduction and Background

Approximately 1 out of 400 children and adolescents in the United States have type 1 diabetes mellitus (T1DM). (1) During 2008–2009, an estimated 18,436 people younger than 20 years in the United States were newly diagnosed with type 1 diabetes annually. (1)

The daily self-management of children and adolescents with T1D is complex and dynamic, requiring frequent self-monitoring of blood glucose (SMBG), insulin injections, and individual meal plans. (2–4) Living with diabetes can feel overwhelming for parents and children, because constant vigilance is required for proper care.

Children with diabetes experience higher rates of depression and other emotional problems than the general population. (5) Although less prevalent than depressive and distress symptoms, there is evidence that children with diabetes are also at elevated risk of anxiety symptoms and have rates estimated between 13–17%. (6) Anxiety can negatively impact children and their families in various ways. Fears of specific diabetes events such as hypoglycemic episodes among children and their parents/caregivers can contribute to heightened levels of stress and general anxiety overall. For the person living with diabetes, any level of increased anxiety is negatively related to the quality of glycaemic control, making diabetes self-management more difficult. (6) Constantly worrying can weigh on children and lead to feeling helpless and being unable to manage diabetes. (6)

Children with T1DM often need support to adequately manage their illness at school; (7) however, the majority of school personnel have an inadequate understanding of diabetes. (8) This can impact both academic performance (9) and quality of life. Previous studies have revealed problems commonly experienced by children and adolescents with diabetes and their parents with regard to restroom privileges, performing SMBG, eating snacks, or administering insulin when needed. (10–12) Children are often asked to leave the classroom to do these self-care functions or to go to the school nurse's office, which can be a long distance from the classroom. (11) It is concerning that children often go unassisted to the nurse's office, which takes them out of the classroom for long periods of time and increases their risk in the event of a diabetes emergency. (11) It is also difficult for children with diabetes to go on field trips and participate in sporting activities or to be given modified school meals. (8, 14)

Concerns about diabetes care at school can be a major stressor for parents of children and adolescents with T1DM. (15,16) Children who reported greater sadness at having diabetes and who believed it was less fair that they had diabetes had higher HbA1c at 6-months. (17) The burden of responsibility that is laid upon the parents could provoke depressive symptoms and may have significant consequences for the care of their child. (8,19) Fears of specific diabetes events such as hypoglycemic episodes among children and their parents/caregivers can contribute to heightened levels of stress and general anxiety overall. For the person living with diabetes, any level of increased

anxiety is negatively related to the quality of glycaemic control, making diabetes self-management more difficult. (3) Constantly worrying can weigh on children and lead to feeling helpless and being unable to manage diabetes. (3)

When given adequate support at schools and the flexibility to performing diabetes care tasks at school, school children generally achieve better diabetes control than children who report less flexibility. (17,20) Moreover, children who can conveniently check their blood glucose levels at school are more likely to participate in all school activities, and their parents are more likely to be satisfied with their child's diabetes care at school. (21)

The American Diabetes Association recently published recommendations for the management of children with diabetes in the school and day care setting. (22) Relevant recommendations include:

- Provide permission for self-sufficient and capable students to carry equipment, supplies, medication, and snacks; to perform diabetes management tasks; and to have cell phone access to reach parent/ guardian and health care provider.
- Allow children and youth should be allowed to provide their own diabetes care at school to the extent that is appropriate based on the student's development and his or her experience with diabetes.
- Encourage independence in older children to make his or her decisions about his or her own care."

The Accu-Chek® Connect Diabetes Management System (DMS) has the potential to address issues and concerns related to safe diabetes management at school. The system automatically uploads blood glucose meter to a smart phone application that then transfers the data to a "cloud" storage platform, which could be accessed and shared between patients, patient caregivers and their healthcare providers in real time. This capability would likely alleviate much of the anxiety and emotional burden associated with diabetes management among pediatric/adolescent patients and their parents and other caregivers. Moreover, the seamless and wireless transfer of patient data in formats that facilitates accurate and efficient identification of glucose patterns will likely enhance the ability of children/adolescents, parents/caregivers and healthcare professionals to utilize the data in meaningful ways, leading to improved clinical and quality of life outcomes.

## **1.2 Study Rationale**

Management of children with type 1 diabetes mellitus (T1DM) requires adult supervision of the child both at home and while away from parents. As children may spend up to one-third of each day away from parents, it is essential that children with T1DM have access to appropriate diabetes care at all times, as well as all adults responsible for managing their care have adequate access to the children's diabetes-related data. The ACCU-CHEK<sup>®</sup> Connect system may provide a platform by which all adults responsible for the management of a child with T1DM have real-time access to that child's diabetes-related data, no matter their location.

Numerous studies have demonstrated the negative impact of inadequate support and failure to adhere to guidelines/federal regulations; however, studies assessing the use of telemedicine technologies with this population are few.

A positive psychosocial impact of ACCU-CHEK<sup>®</sup> Connect DMS use in and around children with T1DM on their parents/caregivers and the children themselves would significantly add to the body of evidence.

Two other studies with the ACCU-CHEK<sup>®</sup> Connect DMS will be initiated in the US during 2015. These will address other elements of management of diabetes by means of the new ACCU-CHEK<sup>®</sup> Connect Diabetes Management System.

In addition to the above, data from this study will be used to support internal development projects including but not limited to development of future ACCU-CHEK<sup>®</sup> devices. Teaching cases may be developed from the data to teach health care professionals techniques.

## 2 Study Design and Duration

### 2.1 Study Design Overview

This is a prospective, interventional, multi-center, post-market, 6-months, cluster randomized study, conducted in the US. In order to maintain a true control group for comparison, the investigational sites will be randomly assigned to one of the following treatments:

- **Interventional Group** ACCU-CHEK® Connect Diabetes Management System
- **Control Group** Usual care: Continued use of subjects' current diabetes devices

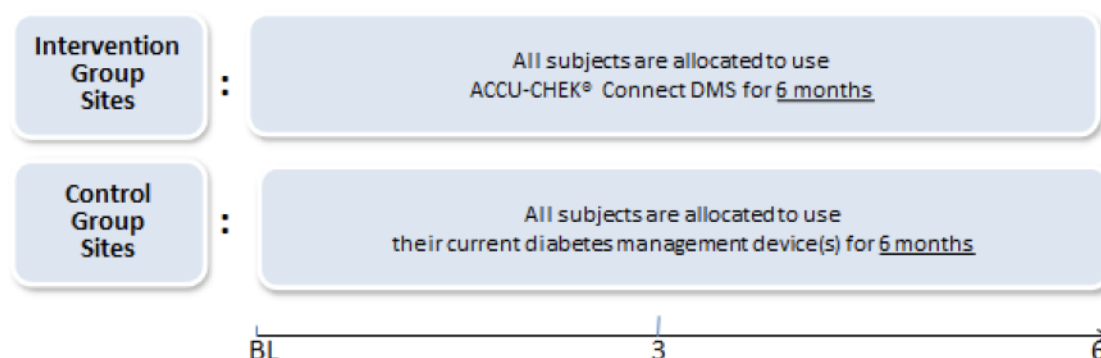


Figure 1 **Study Design**

Between 150 - 200 children with diabetes will be included in the clinical study and the duration of participation is 6 months for each subject. A cluster of 10-20 children is expected to enroll at each investigational site.

All subjects recruited by an Interventional Site will be provided with an ACCU-CHEK® Connect DMS (and up to one additional meter to keep at school), trained in the system's use, and asked to use this system for the following 6 months.

All subjects recruited by the Control site will continue to use their current diabetes management system.

All parents/caregivers independently of the age of their child are also part of the study, and will complete questionnaires about diabetes related stress, system use and other aspects of diabetes.

Furthermore, the health care providers (investigators and study staff) as well as school staff will also be asked to assess their preference in comparison to previously used systems. In order to obtain data prior to study start self-monitored blood glucose (SMBG) data from all subjects will be downloaded at Baseline using Diasend – for the data transfer to the eCRF

During the study the Control sites will continue to download data using Diasend whereas data download at Interventional sites will be managed by ACCU-CHEK® Connect DMS.



Control sites will continue to use data analysis methods according to their current practice for making therapy decision throughout the study. No change in behavior should be introduced by the study in this group and therefore they will not use data downloads via Diasend for therapy decisions, if this is not currently their practice, but they might need to perform downloads via Diasend for eCRF transfer only.

## **2.2 Rationale for the Study Design**

In the light of the increasing Smartphone technology and the launch of several apps to manage health situations other than diabetes, the suite of ACCU-CHEK<sup>®</sup> -devices has been extended with the ACCU-CHEK<sup>®</sup> Connect Diabetes Management System.

Recently, the system has been approved by the FDA.

In order to accompany the launch in the United States, it was decided to conduct a post-market study in school-children with diabetes type 1. The children's parents, the children with diabetes themselves, the investigator and study staff as well as any school staff will be asked assess the ACCU-CHEK<sup>®</sup> Connect Diabetes Management System and any systems in the control group – from several points of view.

In order for all individuals to really get to know the system, and to experience the advantages, we decided to follow each child with diabetes for a total of 6 months.

In order to enable assessment of this user experience with the ACCU-CHEK<sup>®</sup> Connect DMS, a combination of validated patient reported outcome (PRO) - scales and usability/preference questions will be used.

The system is developed for the use in parallel to MDI therapy. Thus, children on pump therapy will be excluded.

Furthermore, we decided to include children and adolescents with diabetes in K-12 grades in full day school setting, aged 6-18 years.

The children and their parents/caregivers will be asked to complete questionnaires to assess diabetes-related distress, family conflict, and affect toward blood glucose monitoring at baseline, 3 month, and 6 month visit.

In addition, the intervention group will complete a questionnaire regarding use, preference, and satisfaction with the ACCU-CHEK<sup>®</sup> Connect DMS at the 6 month visit.

The Sponsor company and their experts are aware that a time away from the usual home setting has an impact on the management of diabetes, and thus, we decided to include a control group in order to enable comparison under same conditions.

### 3 Study Device(s)

#### 3.1 Identification and Description of the Investigational Device:

The **ACCU-CHEK® Connect Diabetes Management System** contains three primary components:

- ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System
- ACCU-CHEK® Connect Diabetes Management App
- ACCU-CHEK® Connect Online Diabetes Management System



**Figure 2** The main components of ACCU-CHEK® Connect Diabetes Management System

#### **ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System**

The ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System is intended to be used for the quantitative measurement of glucose (sugar) in fresh capillary whole blood drawn from the fingertip. The ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System is intended to be used by a single person and should not be shared.

The ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System is intended for self-testing outside the body (in vitro diagnostic use) by people with diabetes at home as an aid to monitor the effectiveness of diabetes control. The ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System should not be used for the diagnosis of or screening of diabetes or for neonatal use.

The ACCU-CHEK® Aviva Plus Test Strips are for use with the ACCU-CHEK® Aviva Connect Blood Glucose Meter to quantitatively measure glucose (sugar) in fresh capillary whole blood samples drawn from the fingertips. This system is intended to be used by a single person and should not be shared. The ACCU-CHEK® Aviva Connect blood glucose monitoring system includes:

- Meter: ACCU-CHEK® Aviva Connect BG Meter with batteries
- Test Strip: ACCU-CHEK® Aviva Plus Test Strips
- Controls: ACCU-CHEK® Aviva Control Solutions

- Lancing Device: ACCU-CHEK® FastClix Lancing Device with lancet drums



Figure 3 ACCU-CHEK® Aviva Connect BG meter

## ACCU-CHEK® Connect Diabetes Management App

The ACCU-CHEK® Connect Diabetes Management App is designed to help:

- Transfer data from your ACCU-CHEK® Connect blood glucose meter.
- Transfer data to your ACCU-CHEK® Connect online diabetes management system account (online account) and optionally share this data with healthcare providers (HCP) or caregivers.
- Receive insulin bolus advice (for those using meal-dosed insulin).
- Perform structured testing.
- Assist in general diabetes management through logging of contextual data.

Note: Each mobile device is different. If the mobile device does not conform to these instructions, consult the mobile device user's manual.



Figure 4 The ACCU-CHEK® Connect Diabetes Management App

## ACCU-CHEK® Connect Online Diabetes Management System

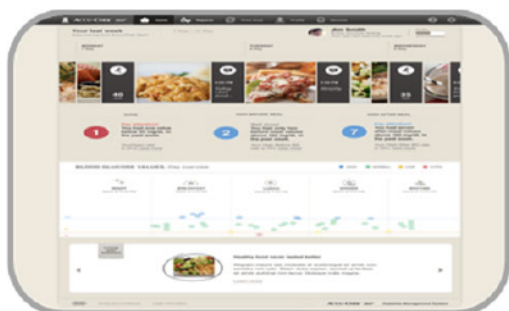
This web-based software supports effective diabetes management for both the healthcare professional and for the person with diabetes. Benefits of the ACCU-CHEK® Connect online diabetes management system include:

- Quick overview of key diabetes therapy indicators
- User-friendly tools for problem identification and data visualization
- Simple upload to online accounts from compatible ACCU-CHEK® blood glucose meters and insulin pumps
- Works in conjunction with the ACCU-CHEK® Connect diabetes management app for mobile devices which includes the ACCU-CHEK® Bolus Advisor and ACCU-CHEK® Connect blood glucose meter (not available in all countries)
- Sharing data from personal accounts to healthcare professional office accounts when both parties have online accounts
- The 3-Day Profile is a tool that guides the person with diabetes through three days of structured testing. This is completed on the app using built-in reminders and viewed in the online accounts. It is clinically proven<sup>1</sup> to reduce HbA1c when used in collaboration with a healthcare professional.



The ACCU-CHEK Connect online diabetes management system includes two types of online accounts:

- A **Personal Account** for the person with diabetes
- An **Office Account** for the healthcare professional



**Figure 5 ACCU-CHEK® Connect online diabetes management system**

### Consumables

The ACCU-CHEK Aviva Plus Test Strips are for use with the ACCU-CHEK Aviva Connect Blood Glucose Meter to quantitatively measure glucose (sugar) in fresh capillary whole blood samples drawn from the fingertips.

The ACCU-CHEK FastClix Lancing Device uses a lancet to obtain a drop of blood from a fingertip. It is designed to make obtaining a drop of blood as comfortable as possible. The lancing device is loaded with a drum containing 6 sterile lancets.

The ACCU-CHEK Aviva Control Solutions contains a known amount of glucose that acts like blood when you apply it to the test strip. Performing a control test lets the user know that the meter and test strips are working properly.

### Status of Documentation of Study Devices(s)

The investigational devices used in this study have received clearance/approval by the FDA.

### Comparative Devices

The subjects randomized to the Control Group will be asked to continue to use their current devices/systems.

## 3.2 Data Download Devices at study sites

At Baseline all sites (both groups) will download SMBG data (from all subjects) in two ways:

- using the existing site process for therapeutic decision
- using Diasend – for the data transfer to the eCRF

During the study the Control sites will continue to download data in these two ways whereas Interventional sites will only use the ACCU-CHEK® Connect DMS.

## 4 Study Objectives

### 4.1 Primary Objective

The primary objective of this study is to assess change in diabetes-related distress among parent/caregiver of school-age children with diabetes (PAID C & T Parent- Questionnaire) after 6 months utilization of the ACCU-CHEK® Connect DMS compared with usual care.

### 4.2 Secondary Objectives

The secondary objectives of this study are to assess the changes in the following measures after 3 and 6 months utilization of the ACCU-CHEK® Connect DMS compared with usual care:

- Change in diabetes-related distress among parent/caregiver. (PAID-C & T Parent Questionnaires) at 3 months compared to Baseline
- Change in diabetes-related distress among school-age children with diabetes. (PAID-C & T Child Questionnaires) at 3 and 6 months
- Change in perceived family conflict among school-age children with diabetes and parent/caregiver. (DFCS-parent and DFCS-youth Questionnaire) at 3 and 6 months
- Change in affect toward blood glucose monitoring (BGM) among school-age children with diabetes and parent/caregiver. (BGMC-parent and BGMC-youth Questionnaire) at 3 and 6 months
- Changes in glycemic control:
  - HbA1c
  - Percentage in Glucose Target Range
  - Glycemic Variability
  - Hypoglycemia

Intervention Group Only at 6 months:

- Use of, Preference, Satisfaction with the ACCU-CHEK Connect DMS
  - Parent/caregiver(s)
  - children/adolescents with diabetes
  - School staff
  - Healthcare Provider (investigator and study staff)

## **5 Selection of Subjects and Investigators**

Investigational sites will be recruited from pediatric endocrinology practices in the US. When the complete cohort of sites have been selected to participate, a random assignment of each site to intervention or control treatment groups will be performed and communicated to the primary investigators.

Subjects will be identified and recruited from the Investigator's (pediatric endocrinology practices) established subject population or from respective group practices using the inclusion criteria; see Section 6.

If a subject and his/her parents/caregivers agree to consider participation in the study, the parents/caregivers will be informed verbally and in writing by means of review of the Informed Consent Form. Time for the possibility to ask questions to authorized study staff will be provided prior to obtaining signatures.

If a subject and his/her parents/caregivers decide to participate, the parents/caregivers shall sign the current IRB approved informed consent form before any study-related procedures;

Children with diabetes will be informed in language according to their age, and asked to sign the assent form before any study-related procedures.

Please refer to Section 12.2.

## 6 Study Population

The targeted study population is school-aged children, age 6-18 years, with type 1 diabetes currently managed by MDI therapy.

All parents/caregivers are also part of the study independently of the age of the child and will be asked to fill out questionnaires.

Recruitment will take place over three months at the site. Subjects will be recruited based on their own/their parents/caregivers' interest to participate in this study as well as verification of subject and parent eligibility through inclusion/exclusion criteria; see below.

### Smartphones

The child/adolescent must currently be using a Smartphone with ability to download the ACCU-CHEK Connect System App accordingly OR able to use a Smartphone provided by the study sponsor exclusively for use in the study.

Specific device compatibility is determined via QR code on the AC Connect meter packaging. When scanned it either takes user to appropriate app-store (compatible device): Google play (Android) or Apple App Store (iOS) or to page that lists the compatible mobile devices.

Compatible phones and devices are continually changing: a compatibility list will be kept.

Number of subjects to be enrolled is between 150 and 200.

Health care providers (investigators and study staff) as well as school staff will also be asked to assess their preference in comparison to previously used systems.

### 6.1 Inclusion Criteria

To be eligible to participate in this clinical study, subjects and their parents/caregivers must meet **ALL** of the respective criteria:

#### Child/adolescent with diabetes

- Diagnosis of type 1 diabetes for  $\geq 3$  months
- Currently managed with multiple daily insulin injections (MDI);
- 6-18 years of age inclusive at enrollment (Visit 1)
- Attending full day school schedule (K-12 grades)
- Able to provide SMBG data minimum of one month prior to study start
- Currently using a compatible Smartphone (see above) with ability to download the ACCU-CHEK Connect System App accordingly OR ability to utilize Smartphone and ACCU-CHEK Connect System App as provided for use in study (Intervention group only)

#### Child/adolescent with Diabetes and Parent(s)/Caregiver(s):

- Informed Consent:
  - Parents/Caregivers provide written informed consent
  - Adolescents (18 years) with diabetes provide written informed consent
  - Child (7-17 years) with diabetes provide age appropriate child assent

- Child (6 years) with diabetes does not provide any assent
- Parent/caregiver currently using a compatible Smartphone with ability to receive SMS/MMS messages
- Able to read and write in English language
- Willing and able to comply with study procedures

## 6.2 Exclusion Criteria

Subjects may not participate in this clinical study if they and/or their parents/caregivers meet **ANY** of the respective criteria:

### Child/adolescent with Diabetes:

- On CSII or intending to transition from MDI to CSII during study period
- CGM use during the course of the study (both home and/or professional CGM)
- Remote data sharing system/device use during the course of the study (i.e. NightScout, DexCom Share, Medtronic Connect)
- Pregnancy
- Diagnosed with any clinically significant condition (e.g. anemia, major organ system disease, infections, psychosis or cognitive impairment);
- Chronic use of steroids in adrenal suppressive doses, other immuno-modulatory medication or chemotherapy

### Parents/Caregivers **and** child with Diabetes

- Visual impairment; preventing the complete use of Connect system
- Parent/caregiver is the investigator or any sub-investigator, general practitioner, practice staff, pharmacist, research assistant or other staff or relative of those directly involved in the conduct of the study and design of the protocol.

## 6.3 Point of Enrollment and Withdrawal

A subject is considered enrolled in the study as soon as

- His/her parents/caregivers have signed the Informed Consent and
- 18 year old with diabetes has signed the Informed Consent (NOTE: parental consent is not required if 18 years of age at time of study entry)
- Child with diabetes has signed age-appropriate child assent
- Child/adolescent with diabetes has been deemed eligible according to above inclusion/exclusion criteria.

A subject is considered withdrawn if he/she was first enrolled, and thereafter one or more of the following occurs:

- Screening failure (any reason).
- Withdrawal of consent to participate in the study.



- Non-compliance with the protocol procedures
- Subject begins CSII therapy during the course of study participation
- Subject begins CGM during the course of study participation
- Subject begins remote data sharing system/device during the course of study participation
- Subject becomes pregnant (self-reported)
- Investigator determines it is not in the best interest of the subject to continue participation in the study.

If any of the above occurs, the Investigator will:

- Ensure subject presents at site accompanied by parents/caregivers in order to ensure complete documentation (Study Completion Form in the eCRF including the date of and reason for early discontinuation and questionnaire), and to return all study materials.

#### **6.4 Replacements**

Subjects who drop-out will not be replaced.

## 7 Visit Schedule, Study Procedures, Training & Data Collection

### 7.1 Visit Schedule

The study consists of the following visits:

- Visit 1 – Baseline                      In office
  - Visit 2 – Week 1                      Phone Call
  - Visit 3 – 12 weeks                      In office
  - Visit 4 – 24 weeks                      In office      Final Visit
  - Visit 5 – 2-5 days after Final Visit      Phone Call in case of ongoing AEs at Visit 4, only
- Please refer to the overall Schedule of Assessments and the below details for each study visit.

### 7.2 Visit 1 - Baseline (Day 1)

Study procedures include the following assessments:

- Obtain written informed consent
  - Parents/caregivers will sign the Informed Consent
  - 18 year old child with diabetes will sign informed consent
  - Children with diabetes will sign age-appropriate assent form
- Check eligibility of Inclusion and Exclusion criteria
- Child/adolescents with diabetes: Perform urine pregnancy test (menstruating females)
- Child/adolescent with diabetes and parents/caregivers: Smartphones; see section 6
- Collect/document the following parameters:

#### Information on the child/adolescent with type 1 diabetes

- Demographics (age/gender/race/ethnicity)
- Obtain and record Diabetes Background and History including insulin therapy, use of CGM, current diabetes devices, use of diabetes management software and Apps, SMBG habits and frequency
- Obtain and record Diabetes Medication, total daily basal dose and average number of boluses per day, sensitivity factors, insulin-to-carb-ratio and target point/range.
- Identify Diabetes Management responsibility (parent/caregiver primarily managing, child self-managing, or child currently transitioning to self-management)
- Communication regarding diabetes parents/caregiver when at school
  - Method: (phone/email/text)
  - Frequency: (multiple times/day, daily, weekly, as needed for problem resolution only).

#### Information on parent(s)/caregiver(s)

- Demographics (age/gender/race/ethnicity/education/job- and marital status)

- Any software, devices or Apps used to monitor child with diabetes remotely
- Communication regarding diabetes with child when at school
  - Method: (phone/email/text)
  - Frequency: (multiple times/day, daily, weekly, as needed for problem resolution only)
- Communication regarding diabetes with school staff
  - Method: (phone/email/text)
  - Primary Contact: (school nurse, teacher, or other school staff)
  - Frequency: (multiple times/day, daily, weekly, as needed for problem resolution only)
- Collect height and weight
- Obtain capillary (finger-stick) blood sample for determination of HbA1c (at central laboratory)
- Administer Questionnaires
  - Intervention Sites: prior to training in the use of ACCU-CHEK® Connect DMS
  - Control Site(s): prior to general study instructions
- Record brand of current BG meter and serial number
- Download SMBG data using existing site process and discuss SMBG download with patient and parent/caregivers and collaboratively agree on therapy changes (pharmacologic and/or behavioral) and modify SMBG regimen, if needed.
- Download current BG meter using Diasend for eCRF data
- Schedule appointment for week one phone call (Visit 2) and 3 months (Visit 3)
- Record number of days missed from work (parent/caregiver)/school (child with diabetes) that are diabetes related in previous 3 months and indicate reason (doctor appointments, illness or other).
- Discuss and record current prescribed therapy (pharmacologic and/or behavioral) and prescribed SMBG regimen.
- Record any adverse events (AEs) since last visit if not done immediately
- Record all relevant data in the eCRF

#### Intervention Sites, only

- Dispense ACCU-CHEK® Connect DMS and record serial number of BG meter(s)
- Dispense Smartphone to child/adolescent (if applicable)
- Set up ACCU-CHEK® Connect DMS for connectivity, portals & invitations
- Provide training in the use of the system
- register current operating system of smart phone with version number
- Dispense Call Center Card and instruct in reporting of malfunctions/complaints with ACCU-CHEK® devices



### **7.3 Visit 2 – Phone Call one week after Visit 1**

Study procedures include the following assessments:

- Record any adverse events (AEs) since last visit, if this has not been done immediately
- Record malfunctions/complaints of any device, if any
- Intervention group: Follow-up with parents/caregivers and child with diabetes to identify issues/obstacles associated with system in use
- Record all relevant data in the eCRF

### **7.4 Visit 3 - 12 weeks after Visit 1**

Study procedures include the following assessments:

- Record any malfunctions/complaints, of device as applicable
- Assess and record any new AE, if this has not been done immediately and/or changes to ongoing AE/SAEs since the previous visit.
- Download child's BG data and review
  - Intervention Sites: review ACCU-CHEK Connect Diabetes Management data
  - Control Site(s) review usual care SMBG data
- Discuss SMBG download with patient and parent/caregivers and collaboratively agree on therapy changes (pharmacologic and/or behavioral) and modify SMBG regimen, if needed.
- Discuss any change in software, devices, or apps used to manage diabetes or monitor child w/diabetes remotely
- Collect height and weight
- Record number of (diabetes related) days parents/caregivers missed from work and child with diabetes missed from school since last visit; indicate reason (doctor appointments, illness or other)
- Obtain capillary (finger-stick) blood sample for determination of HbA1c (at central laboratory)
- Intervention Group: Follow-up with parents/caregivers and child with diabetes to identify issues/obstacles associated with system in use
- Control Group: Download current BG meter using Diasend for eCRF data
- Have child and his/her parents complete Questionnaires
- Make appointment for the last Visit, Visit 4 – 6 months after Visit 1
- Record all relevant data in the eCRF

### **7.5 Visit 4 - Final Visit - 24 weeks after Visit 1**

Study procedures include the following assessments:

- Record any malfunctions/complaints, of any device as applicable

- Assess and record any new AE/SAEs and/or changes to ongoing AE/SAEs since the previous visit.
- If ongoing AE/SAE; schedule appointment for a Follow-up call in 2-5 days
- Download child's BG data and review
  - Intervention Sites: review ACCU-CHEK Connect Diabetes Management data
  - Control Site(s) review usual care SMBG data
- Discuss and record any therapy changes (pharmacologic and/or behavioral) and modify SMBG regimen, if needed.
- Discuss any change in software, devices, or apps used to manage diabetes or monitor child w/diabetes remotely
- Collect height and weight
- Record number of (diabetes related) days parents/caregivers missed from work and child with diabetes missed from school since last visit; indicate reason (doctor appointments, illness or other)
- Obtain capillary (finger-stick) blood sample for determination of HbA1c (at central laboratory)
- Intervention Group: Follow-up with parents/caregivers and child with diabetes to identify issues/obstacles associated with system in use
- Control Group: Download current BG meter using Diasend for eCRF data
- Have child and his/her parents complete Questionnaires
- Have child/parents/caregivers return smartphones, if these had been provided at the beginning of the study
- Record all relevant data in the eCRF

## 7.6 Visit 5 - Follow-up Call

This follow-up phone call takes place 2-5 days after the study end. Study procedures include the following:

- Assess and record any changes to AE/SAEs which were ongoing at **Visit 4 (Final Visit)**.
- Record all relevant data in the eCRF

## 7.7 Unscheduled Study Visits or Phone Calls

During the course of the study, subjects may require additional (unscheduled) visits with their physicians (Investigators) for any number of reasons including, but not limited to the following:

- Diabetes medication/therapy adjustments
- Assess whether ACCU-CHEK® Connect data provided by the patient was sufficient to make informed decisions regarding patient therapy adjustment.
- Adverse Events such as, but not limited to:
  - Common respiratory infections including colds and flu.
  - Urinary tract infections.
  - Gastrointestinal disturbances.
  - Depression.
  - Minor injuries.

For tracking purposes and future analysis of the potential cost effectiveness, any additional study visits will be documented as **Unscheduled Visits** in the electronic case report form (eCRF).

Any conditions like above should be documented under Adverse Events.

Any changes to medication should be documented, as follow:

- Insulin (any changes in doses or parameters) under Diabetes Medication

Full documentation of the visit including any assessments or examinations performed should be maintained in the source documents; including:

- Person requesting unscheduled visit
- Reason for unscheduled visit
- If visit is remote or in-office
- Type of remote visit (i.e. telephone, email, text, video chat, etc.)
- Action taken during consult
- Source of data utilized for consult (i.e. electronically sent reports, web portal, verbal, etc.)
- Therapy/device/SMBG changes made as a result of remote visit
- Any change in software, devices, or apps used to manage diabetes or monitor child w/diabetes remotely

## 7.8 Training of Subjects

In order to prepare subjects as well as their parents/caregivers for the study procedures, they will be trained at the Baseline Visit (Visit 1) in the following:

Intervention Group:

The children with diabetes as well as their parents/caregivers will be trained in the following:

- use and functionalities of the ACCU-CHEK® Connect DMS.
- reporting of malfunctions/complaints via the Call Center
- general study procedures

#### Control Group:

The children with diabetes as well as their parents/caregivers in this group will only be trained in general study procedures, as the children continue to use their previous diabetes management system.

## **7.9 Questionnaires**

Children with diabetes and their parents/caregivers will be asked to complete the following Questionnaires:

- Visit 1 (Intervention group to complete prior to receiving training for ACCU-CHEK® Connect DMS):
  - Parents/Caregivers (independently of age of the child)
    - PAID - Parent to Child or Teen - dependent on age of child with diabetes
    - BGMC - parent
    - DFCS - parent
  - Adolescent/Teen with diabetes (12-18y)
    - PAID - Teen
    - DFCS - youth
    - BGMC - youth
  - Child with diabetes (8-11y)
    - PAID - Child
    - DFCS - youth
    - BGMC - youth
- Visit 3:
  - Parents/Caregivers (independently of age of the child)
    - PAID - Parent to Child or Teen - dependent on age of child with diabetes
    - BGMC - parent
    - DFCS - parent
  - Adolescent/Teen with diabetes (12-18y)
    - PAID-Teen
    - DFCS - youth
    - BGMC - youth

- Child with diabetes (8-11y)
  - PAID - Child
  - DFCS - youth
  - BGMC - youth
- Visit 4:
  - Parents/Caregivers (independently of age of the child)
    - PAID - Parent to Child or Teen –(dependent on age of child with diabetes)
    - BGMC - parent
    - DFCS – parent
    - Questionnaire about Use, Preference, Satisfaction (Intervention Group Only)
  - Child/Adolescent/Teen with diabetes (12-18y)
    - PAID - Teen DFCS - youth
    - BGMC – youth
    - Questionnaire about Use, Preference, Satisfaction (Intervention Group Only)
  - Child with diabetes (8-11y)
    - PAID - Child
    - DFCS - youth
    - BGMC – youth
    - Questionnaire about Use, Preference, Satisfaction (Intervention Group Only)

Healthcare Providers, School Staff of the intervention group will be asked to complete the Questionnaires about Use, preference, Satisfaction

All Questionnaires will be completed through the eCRF set-up in the Marvin-system; see section 7.11.

## 7.10 Central Laboratories

Central lab will be utilized for the determination of:

- HbA1c at Visit 1, 3 and 4.

For details regarding tubes, labeling, packaging, dispatch to central laboratory, please refer to the Central Laboratory Handbook.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] USA

[REDACTED]

## 7.11 Data Collection

A **Subject Screening and Enrolment Log** will be completed for all subjects whose parents/caregivers have provided their informed consent i.e., signed the Informed Consent Form - with the reasons for non-eligibility, if applicable.

### eCRF

An eCRF has been set up in the Marvin system, provided by [REDACTED] Germany.

For each subject who has signed the Subject Informed Consent Form, the Investigator must allocate a **subject ID number** via the eCRF-system of two digits for the site and three digits for the subject: **SS-XXX**.

For each enrolled subject, an eCRF must be completed (throughout the study) and electronically signed by the Principal Investigator or Sub-/ Co-Investigator (at the end of the subject's participation in the study).

Upon training, Investigators and authorized study staff will enter subject data during or shortly after the respective visits.

### Data Discrepancy Management

Subsequently, the entered data will be systematically checked:

- by means of pre-defined computerized validation checks (as outlined in the Data Management Plan)
- by data review by the Sponsor including but not limited to the Data Manager, Monitor and Study Manager.

All data discrepancies will result in data queries within the eCRF-system, which must be addressed (data confirmed or changed) by the study site staff and closed by the originator.



In addition, protocol violations and deviations must be recorded in the eCRF throughout the study, and documented further via the query-system, as applicable (see Section 14).

If a subject withdraws from the study, the reason must be recorded on the eCRF.

### **Subject and Parent/Caregiver Questionnaire**

Subjects and their parents/caregivers will be asked to complete a questionnaire at Visits 1, 3 and 4, see Section 7.9. These questionnaires will be presented via the site's provided study laptop.

At the first login, the subject is asked to define and enter a new password.

As soon as the subject has completed the questionnaire(s), he/she should close the entry screen by clicking the red "Log-out" button at the upper right corner.

For the sake of confidentiality, neither the Investigator nor other study staff will be able to read the subject's entries.

### **HCP and School Nurse Staff Questionnaires**

For Intervention Group sites only, the HCP (Site Investigator and School Nurse/staff (if available)) will be asked to complete a Questionnaire.

### **Measures arising from sources other than questionnaires**

Glycemic Control: HbA1c levels - at Baseline, visit 3 and 4 – analyzed by central lab

- Data from ACCU-CHEK® Connect BG-meters:
  - Change in SMBG habits and frequency (Baseline and Visit 4)
  - Percentage in Glucose Target Range, above and below Glucose Target Range
  - Glycemic Variability
  - Hypoglycemia
- Data from ACCU-CHEK® Connect DMS and eCRF entries:
  - Assessment by HCP whether Accu-Chek Connect data provided by the patient was sufficient to make informed decisions regarding patient therapy adjustment.

SMBG data and other diabetes-related data from ACCU-CHEK® Connect system is planned to be uploaded into the eCRF during the study and after study completion. The mapping of these device data to the correct subject with diabetes will be an automated de-identification process for saving the device data with the subject data.

### **Database Closure**

Quality control of the database will be made throughout the study conduct in order to prepare the database closure. After the database has been declared clean (i.e. complete and accurate), the database will be locked.

Any changes to the database after that time can only be made by joint written agreement between the Study Manager and the Statistician.

### **7.12 Medical Care after Study Participation**

Upon the subject's termination (premature or planned) in the clinical study, it is up to the subject him/herself and the parents/caregivers, preferably in agreement with the treating physician, to determine their future treatment needs from the following options:

- return to the device used prior to the study or
- start/continue with ACCU-CHEK® Connect DMS
- use any other suitable device available on the market



## 8 Risk/Benefit Analysis of the Investigational Device and Clinical Investigation

### 8.1 Potential Risks

During participation in this clinical study, subjects may encounter the following known potential risks of diabetes management therapy:

- Possible hypoglycaemia.
- Possible hyperglycaemia which might progress to ketosis and diabetic ketoacidosis (DKA).
- Mild discomfort and soreness, risk of infection from multiple finger sticks
- Anxiety over recording SMBG values that maybe out of the expected target ranges.

The above risks are an integral part of diabetes therapy and applied in daily practice. It has to be underlined that subjects face the same risks as listed during their routine therapy. The likelihood of serious events occurring is considered uncommon.

### 8.2 Minimization of Risks

The Sponsor has minimized the potential of the above risks to occur by:

- Selection of qualified Investigators consulting study subjects during the scheduled visits.
- Selection of subjects, parents/caregivers experienced in diabetes management therapy
- Subjects are advised not to change their current MDI diabetes therapy without consulting their physician (Investigator).

### 8.3 Potential Benefits

The study subjects and their families may experience the following potential benefits while participating in this study:

- Subjects and their families may be motivated to learn more about diabetes and to have better discussions of potential issues with their health care providers.
- Subjects and their families may gain personal satisfaction and decreased diabetes distress from participating in this study.
- Subjects may reduce their HbA1c from participating in this study
- The following will be provided during the study at no charge to subjects and their families:
  - ACCU-CHEK® Connect Diabetes Management App
  - ACCU-CHEK® Aviva Connect BG Meter and consumables
  - Smartphones, if applicable
- At study completion, subjects and families in the intervention group may elect to keep and use the investigational device; except the study provided Smartphone, if applicable. Regardless of group assignment each family will receive a [REDACTED] gift card for the completion of Visit 1, 3 and 4 (total [REDACTED] if [REDACTED] all visits [REDACTED] completed).

## **9 Adverse Events Recording and Reporting**

### **9.1 Definitions of Adverse Events**

The definitions are based on ISO 14155:2011(E) and respective sections CFR Title 21 for Medical Device Studies.

#### **9.1.1 Adverse Event**

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

In addition, this definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to investigational medical devices.

#### **9.1.2 Serious Adverse Event**

A Serious Adverse Event (SAE) is any AE that fulfils at least one of the following criteria:

- Led to death.
- Led to a serious deterioration in the health of a subject resulting in:
  - A life-threatening illness or injury, or
  - A permanent impairment of a body structure or a body function, or
  - An in-patient or prolonged hospitalization, or
  - A medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
- Foetal distress, foetal death or a congenital abnormality or birth defect.

A planned hospitalization for a pre-existing condition, or a procedure required by the study procedure, without serious deterioration in health, is not considered an SAE.

## **9.2 Definition of Hypoglycemia, Hyperglycemia Episodes and Diabetic Ketoacidosis**

Hypoglycemia and hyperglycemia can be symptomatic or asymptomatic and are subset of AEs occurring within Diabetes studies.

Any hypoglycemia or hyperglycemia episode which occurs during the course of the study will be documented by the subject him-/herself in his/her individual Subject Diary, if applicable, or will be defined specifically by the study procedure e.g. in the visit description of this study protocol.

### **9.2.1 Asymptomatic Hypoglycemia Episode**

An asymptomatic hypoglycemic episode is defined as a low blood glucose reading below 70 mg/dL (3.9 mmol/L) without symptoms and is considered as a non-captured expected AE described in Section 9.3.1.2.

### **9.2.2 Symptomatic Hypoglycemia Episode**

A symptomatic hypoglycemia episode is defined as an AE with symptoms consistent with hypoglycemia and may be confirmed by blood glucose readings below 70 mg/dL (3.9 mmol/L).

Symptoms might include but are not limited to: sweating, dizziness, light-headedness, tremors, nervousness, hunger, headaches, weakness or tiredness.

Symptomatic hypoglycemia is considered an expected and captured AE, as described in Section 9.3.1.1.

### **9.2.3 Severe Hypoglycemia Episode**

A severe hypoglycemia episode is defined as symptoms in loss of consciousness and/or seizures resolving upon administration of glucose or glucagon by another person (only third party assistance). A blood glucose value below 36 mg/dL (2.0 mmol/L) might be available, but is not mandatory (if no assistance, then not considered Severe Hypoglycemia).

Such episodes are defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or be faxed).

### **9.2.4 Hyperglycemia Episode**

Hyperglycemia is defined as high blood glucose readings, a recommended threshold to intervene could be defined as values above 240 mg/dL (13.3 mmol/L). However, investigators should consider the condition of the individual subject.

Only hyperglycemia episodes in combination with medical intervention or additional diagnostic procedures have to be documented as AE in the eCRF, as described in Section 9.3.1.1.

### **9.2.5 Diabetic Ketoacidosis**

Diabetic Ketoacidosis is defined as any symptoms such as polydipsia, polyphagia, polyuria, nausea, or vomiting; and presence of serum ketones, or moderate or large urinary ketones; and either arterial blood pH <7.3 or serum bicarbonate <15 mg/L and treated as directed by the subject's physician.

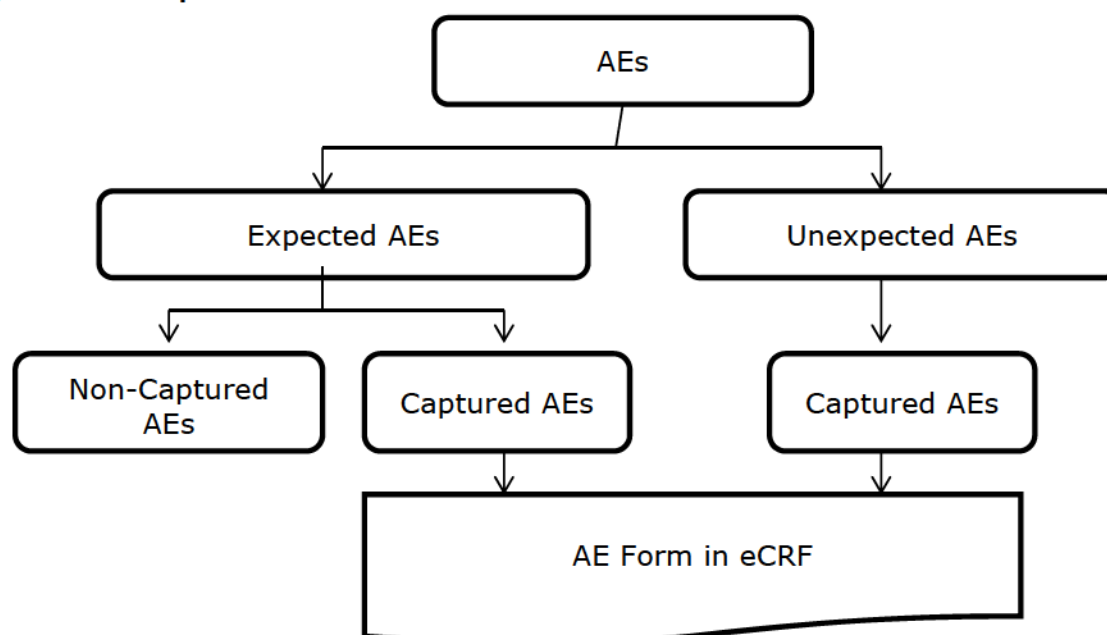
Such episodes are also defined as SAEs and, thus, they must follow the SAE reporting pathway via the eCRF (or be faxed).

## **9.3 Expectedness Classification of Adverse Events**

An AE will be classified as either expected or unexpected (see Figure 6).

For the purpose of this study, expected AEs will be divided into non-captured and captured AEs. These distinctions were made based on the frequency of occurrence, severity of event, and risk to subject. All captured AEs will be documented in the eCRF.

**Figure 6 Expectedness Classification of Adverse Events**



Abbreviations: AE = adverse event; eCRF = electronic Case Report Form.

## 9.3.1 Expected Adverse Events

### 9.3.1.1 Captured Expected Adverse Events

The following expected AEs may occur at any time in the course of managing diabetes. Immediate or short term risks to subjects from some of these expected AEs are higher than those identified under Non-Captured Expected AEs.

Therefore, for the purposes of this study, the following expected AEs will be considered captured expected AEs and the AE Form in the eCRF needs to be completed:

- Symptomatic hypoglycemia episodes (see Section 9.2.2).
- Hyperglycemia in combination with medical intervention..
- Ketosis and ketoacidosis.

These captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values or otherwise as instructed by the Investigator.

### 9.3.1.2 Non-Captured Expected Adverse Events

Non-Captured expected AEs may occur at any time in the normal course of managing diabetes. For the purpose of this study, they will be considered as non-captured expected AEs and will not be documented in the eCRF, these include:



- Asymptomatic hypoglycemia episode (see Section 9.2.1).
- Hyperglycemia without medical intervention.
- In the event of a sore finger, subjects will be advised to avoid taking self-monitoring blood glucose samples from that finger.
- In the event of a mild infection at a lancing site, the study subject will be reminded to wash hands before all blood tests and encouraged to consult their nurse or physician on the management of an infection.

Since these non-captured expected Adverse Events identified above are common as well as expected and pose minimal immediate risk to the subjects, they will not be tracked and logged as AEs during the course of the study. Investigators may log reports of these non-captured expected AEs as is customary within their practice.

These non-captured expected AEs will be handled as follows:

Subjects will be instructed to follow their personal physicians' instructions for management of low and high blood glucose values as well as for minor skin damage, minor bleeding and mild discomfort.

### **9.3.2 Unexpected Adverse Events**

All AEs which do not meet the criteria mentioned under expected AEs (Section 9.3.1) are considered as unexpected AEs and will be documented in an AE Form in the eCRF.

## **9.4 Assessment of Causality in Relationship to Device**

### **9.4.1 Related**

An AE is deemed related with a device if **ALL** of the following criteria apply:

- There is a reasonable temporal sequence between AE and use of the device.
- It follows a known or expected response pattern of the device.
- It cannot be reasonably explained by the known characteristics of subject's clinical state.

Adverse events resulting from insufficiencies and/or inadequacies in the instructions for use or the deployment of the device will be classified as related.

Adverse events resulting from a user error will be classified as related.

### **9.4.2 Possibly Related**

An AE is deemed possibly related if:

- There is a reasonable temporal relationship between the AE and use of the device; and
- It follows a known or expected response pattern of the device but could have been easily produced by a number of other aetiologies.

### 9.4.3 Unrelated

When there is no reasonable temporal association between the device and the AE or the event was related to the subject's clinical state or concomitant treatment(s).

### 9.4.4 Not Assessable

When there is not sufficient information to assess a relationship.

## 9.5 Period of Observation

All AEs ongoing at the time of study termination - irrespective their severity - should be followed up - via telephone - for a maximum of 5 days after the subject's last visit to the site. A medical statement should be included in the AE Form in the eCRF for all ongoing AEs after the Period of Observation.

## 9.6 Investigators' Responsibility to Report Serious Adverse Events

Investigators must immediately report all SAEs on the SAE Report Form which has been integrated in the eCRF - irrespective of expectedness or relationship to study procedures or study devices.

For reported deaths, the Investigator should provide any additional information, as requested and required, such as autopsy reports or terminal medical reports.

The Investigator should complete and (electronically) sign the form, and send it (electronically, within the eCRF system) to:

**Study Safety Officer:** [REDACTED]

In case, the eCRF system is not functioning, a paper version of the form should be completed by hand, signed and sent as described above (faxed or e-mailed).

If SAE/SADE information is unsatisfactory and essential data is missing, the Investigator is requested to conduct the necessary follow-up actions and/or to provide additional information as soon as possible.

## 9.7 Sponsor's Responsibility to Report Serious Adverse Events/Serious Adverse Device Effects

The below Study Safety Officer is responsible for all safety related topics of the study:

Name:

Email:

Phone:

Fax:



Upon receipt of an SAE Report Form, the Study Safety Officer will:

- Review the SAE Report Form for completeness and make a medical assessment.
- Ensure that additional (initially, follow-up and final) information is obtained and communicated, as applicable.

After Safety Assessment the SAE is reported, as applicable, via the following internal lines:

Roche Q-Function is responsible for reporting of initial, follow-up and final SAE reports to:

- Regulatory Authorities.

Study Manager or designee is responsible for reporting to:

- Institutional Review Boards (IRB)
- Other Investigators.



## **10 Malfunction/Complaint Reporting Process**

The FDA cleared medical device (ACCU-CHEK® Connect Diabetes Management System) observed in this study is used within the Intended Use. This is also valid for possible ACCU-CHEK® BG meters used by the Control group during the first 3 months of the study.

### **Accu-Chek® Customer Care - Call Center Cards**

Roche Diabetes Care, Inc. will provide the Investigator, including the study site staff, with a template of the Accu-Chek® Call Center Card containing the Accu-Chek® Customer Care Service Center phone number, study name and Roche Diabetes Care, Inc. internal study number.

The study staff will distribute the Call Center Card when the Roche product is dispensed to study participants. Study subject(s) and parents/caregivers should be instructed to use this card when contacting the Accu-Chek® Customer Care Service Center to identify that they are participating in a Clinical Study using Roche products. The information requested by the Accu-Chek® Customer Care Service Center will enable Roche Diabetes Care, Inc. to meet its reporting obligations.

Subjects and parents/caregivers will be instructed to report any malfunctions/complaints to the Accu-Chek® Customer Care Service Center as described above, for the Roche product. Subjects may also have the option to report malfunctions/complaints to their Investigator during a study visit, whereby the Investigator and subject contact the Roche Diabetes Care, Inc. Accu-Chek® Customer Care Service Center together, to identify the subject is participating in a Clinical Study using Roche products. Contact details will be noted on subject's identification card.

## **10.1 Definitions**

### **10.1.1 Definition of Malfunction**

A "malfunction" is a failure of the device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

### **10.1.2 Definition of Complaint**

Complaint means any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a device after it is released for distribution. 21CFR 820.3(b)

## 11 Statistical Considerations and Data Analysis

The primary and secondary analysis as defined in this study protocol will be described in the Statistical Analysis Plan (SAP) and summarized in the final Clinical Study Report (CSR). All additional exploratory analyses required for publications or requested for different needs will be included in a separate Appendix e.g. Publication Analysis Plan (PAP). This might include any ad-hoc additional analyses not defined in the final version of the study protocol/amendment and the SAP.

### 11.1 Null Hypothesis and Sample Size Calculation

The primary outcome variable is change from baseline in PAID-C & T Parents at 6 months. A sample size of 75 patients per group will have 80% power ( $\alpha=0.05$ , 2-sided) to detect a treatment effect size of 0.460. Given assumptions of common SD from 5-16, this sample size would be able to detect treatment group differences of 2.3 to 7.4, respectively. In order to account for possible drop-out prior to the 6 month endpoint, 100 subjects per group will be enrolled.

### 11.2 Populations for Analysis

The intent-to-treat (ITT) population will consist of all families that have completed at least one questionnaire at both baseline and end of study.

The full analysis set (FAS) will consist of all families that have completed the parent/caregiver PAID-PR questionnaire at both baseline and end of study.

The safety population will consist of all subjects.

### 11.3 Subject Demographics and Baseline Characteristics

#### Child/Adolescent with diabetes

- Demographics (age/gender/race/ethnicity)
- Collect and record most recent HbA1c including date of measurement.
- Obtain and record Diabetes Background and History including insulin therapy, previous personal CGM, SMBG habits and frequency and diabetes complications
- Obtain and record Diabetes Medication including but not limited to brand name(s) of insulin used, total daily dose, total basal and bolus doses, sensitivity factors, etc.
- Identify Diabetes Management responsibility (parent/caregiver primarily managing, child self-managing, or child currently transitioning to self-management)
- Communication regarding diabetes parents/caregiver when at school
  - Method: (phone/email/text)
  - Frequency: (multiple times/day, daily, weekly, as needed for problem resolution only).
- Number of missed school days in past 3 months (diabetes-related)



**Parent / caregiver**

- Demographics (age/gender/race/ethnicity/education/job- and marital status)
- Communication regarding diabetes with school staff
  - Method: (phone/email)
  - Primary Contact: (school nurse, teacher, or other school staff)
  - Frequency: (Multiple times/day, daily, weekly, as needed for problem resolution only)
- Number of missed work days in past 3 months (diabetes-related)

All subject characteristic variables will be summarized descriptively. Continuous variables will be summarized in terms of descriptive statistics including the number of subjects (N) without missing values, mean, standard deviation (SD), and range

Categorical variables will be summarized in terms of absolute frequencies and percentages. In general, the denominator for the percentage calculation will be based upon the total number of subjects in the study population, unless otherwise specified.

**11.4 Primary Objective Analysis**

Change in diabetes-related distress in parents/caregivers of children who utilize the ACCU-CHEK® Connect Diabetes Management system compared to the change observed in the Control Group. Diabetes related distress will be measured via the PAID- C & T parent questionnaires which will be administered Pre and Post Study Participation.

A change in the total PAID-C & T parent score between pre and post study will be calculated and compared between groups utilizing with treatment group as the independent variable, and covariates such as baseline PAID, and child demographic and diabetes history variables.

Descriptive statistics for observed and change from baseline scores, and 2-sample t-tests will be presented at both 3 and 6 month visits. This analysis will be performed on the Full Analysis Set population.

**11.5 Secondary Objective(s) Analysis**

The following secondary objectives will be analyzed by comparing the Pre-Post changes in questionnaire scores from subjects utilizing the ACCU-CHEK® Connect Diabetes Management system with changes from those subjects in the Control Group. Pre, Post, and Change scores will be calculated for each group and summarized by descriptive statistics. The change scores will be compared between groups utilizing both ANCOVA methods described above, and with 2-sample t-tests. These analyses will be performed on both the FAS and the ITT populations.

- Change from baseline in PAID- C & T parent at 3 months in parents/caregivers.
- Change from baseline in diabetes-related family conflict in parents/caregivers as measured by DFCS questionnaires at 3 and 6 months

- Change from baseline in attitudes toward blood glucose monitoring in parents/caregivers as measured by BGMC-parent questionnaire at 3 and 6 months.
- Change from baseline in diabetes-related distress among school-age children as measured by the PAID- C & T child questionnaires at 3 and 6 months.
- Change from baseline in perceived family conflict among school-age children measured by the DFCS-youth questionnaire at 3 and 6 months.
- Change from baseline in affect toward blood glucose monitoring (BGM) among school-age children as measured by the BGMC-youth questionnaire at 3 and 6 months.
- Change from baseline in perceived family conflict in parent/caregiver as measured by DFCS-parent questionnaire at 3 and 6 months.
- Changes from baseline in glycemic control at 3 and 6 months defined as:
  - HbA1c
  - Percentage in Glucose Target Range
  - Glycemic Variability
  - Hypoglycemia
- The secondary objectives of ease of use, satisfaction, and preference for using the **ACCU-CHEK® Connect Diabetes Management System** compared with previous systems will be analyzed by summarizing the end of study outcomes from the following participant groups within the intervention group:
  - Parent
  - Children
  - School staff
  - Healthcare Provider (s)

Each question from this Post Questionnaire will be summarized separately utilizing descriptive statistics of the numerical scale value of the question (mean, standard deviation, range and 95% CI), and the distribution of values (number and percent of respondents at each level of response). These analyses will be performed on both the FAS and the ITT populations

## 11.6 Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Only AEs occurring after the start of the ACCU-CHEK® Connect Online Diabetes Management System will be included in the AEs tables.

Summaries of incidence rates (frequencies and percentages) of individual AEs by MedDRA System Organ Class and Preferred Term will be prepared. Such summaries will be displayed for all AEs, AEs by maximum severity, AEs by strongest causality to study device (and any associated pump devices), and AEs leading to withdrawal of study device.

Deaths, other SAEs and AEs leading to withdrawal will be listed separately.

Episodes (numbers) of the following AEs will be summarized:

- Symptomatic hypoglycaemia
- Severe hypoglycaemia (SAEs)

- Diabetic Ketoacidosis (SAEs)

### **11.7 Interim Analysis**

No interim analysis will be conducted on the primary objective. Nevertheless a “data pull” analysis will be conducted at a suitable timepoint.

## **12 Ethical and Legal Considerations**

### **12.1 Statement of Compliance**

The study will be performed in accordance with the principles stated in the current version of World Medical Association's Declaration of Helsinki "Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects", that are consistent with the principles outlined in the ICH Guideline on GCP where it applies to medical devices and the applicable national regulations for medical device law and applicable ordinances, FDA 21 CFR Parts 11, 50, 54, 56, 803, 812, 814 and 820.30, as applicable in each participating country.

### **12.2 Subject Informed Consent**

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written Subject informed consent – before any study procedures – from each subject considering participation in this study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study – orally as well as presented in the written Subject Informed Consent.

The Investigator or designee (if applicable) must also explain that the subject is completely free to refuse to enter the study or to withdraw from the study at any time, for any reason and could return to standard care.

The Investigator or authorized staff must document the date of each subject's informed consent in the respective eCRF.

If any new safety information results in significant changes in the risk/benefit assessment, the Informed Consent Form should be reviewed, updated and re-submitted to the IRB for approval.

Subjects already participating in the study should be informed of the new information, and asked to give their written informed consent to continue in the study.

New subjects shall only receive the updated documents.

All subjects will be given a copy of the signed Subject Informed Consent Form(s).

### **12.3 Confidentiality of Study Documents and Subject Records**

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On the eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by a unique study identification code, i.e. Subject ID (Number).

The Investigator will keep a **Subject Screening and Enrolment Log** linking study identification codes, and subject contact information. The Investigator will maintain these study documents e.g. subjects' written informed consent forms, in strict confidence and as part of the Investigator's Site File.



Any data obtained from subjects participating in the study may be used to build case studies for educational purposes and all identifying data will be completely removed or blacked-out for these purposes.

## **12.4 Data Protection**

The subject and their parent/caregivers will be informed of their right of access, objection and correction of the data recorded during this study, and that this right may be exercised at any time through his/her physician.

Information relating to participating physicians will be declared and the physicians will be informed – within the framework of their agreement – of their right to access, object to and correct this information.

## **12.5 Institutional Review Board (IRB)**

This protocol and any accompanying material provided to the subject (such as subject information sheets or descriptions of the study used to obtain informed consent) as well as any advertising used or compensation given to the subject, will be submitted by the Investigator to an IRB. Approval from the committee must be obtained before starting the study, and should be documented in a letter to the Investigator specifying the date on which the committee met and granted the approval. Any modifications made to the protocol after receipt of the IRB approval must be re-submitted by the Investigator to the Committee in accordance with local procedures and regulatory requirements.

## **12.6 Regulatory Authorities**

Submissions and/or notification to Regulatory Authorities will be performed as required by local legislation in each participating country for this type of study.

## **12.7 Amendments to the Clinical Study Protocol**

Study protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the Investigator. These modifications must be prepared by a representative of the Sponsor and initially reviewed and approved by the appropriate representatives of the Sponsor and Statistician.

All study protocol modifications must be submitted to the appropriate IRB for approval in accordance with local procedures, and Competent/Regulatory Authorities as required. Approval must be granted in writing before any changes can be implemented, except for those changes necessary to eliminate an immediate hazard to the subjects, or when the change(s) involve only logistical or administrative aspects of the study (e.g. change in Monitor, change of telephone number). Note: these changes will be re-submitted for IRB review and approval as soon as possible.



## 12.8 Suspension or Premature Termination of the Clinical Study

Both the Sponsor and the Investigator reserve the right to terminate the clinical study at any time. Should this be necessary, the parties will arrange the procedures on an individual basis after review and consultation. The only reason for early termination of the study by the Sponsor would be the occurrence of unexpected safety or ethical consideration for the protection of the subject's interests. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the subject's interests.

## 12.9 Record Retention


In order to comply with Roche Diabetes Care requirements, Investigators must maintain all required essential documents – in the Investigator Site File – at the site for at least 15 years after the study ends.

Essential study documents are those documents which individually and collectively permit evaluation of the conduct of the trial and the quality of the data produced – stored before during and after the study conduct in the Investigator's Site File. They include but are not limited to, those pertaining to subject files and other source data (e.g. hospital files, consultation records, laboratory reports, etc). The Investigator should ensure that the Investigator Site File is stored in a secure location and should take measures to prevent accidental or premature destruction of any documents.

The Investigator must contact the Sponsor for approval prior to discarding any study-related documents, even if retention requirements have been met.

If the Investigator leaves the clinical site at which the study has been conducted, he/she or current representative must contact the Sponsor to make suitable arrangements to ensure that the study records, including a copy of the **Screening and Enrollment Log** are retained as specified above and to provide for the continuing access to the records by Sponsor representatives and Regulatory Authorities.

## 12.10 Reimbursement, Indemnity and Insurance

Subjects will receive a  gift card for the completion of every in clinic visit (Visit 1, 3 and 4)

Reimbursement, indemnity and insurance shall be addressed in a separate agreement agreed upon by the parties.

## 12.11 Publication of Data and Protection of Trade Secrets

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to Roche Diabetes Care prior to submission. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

Any formal publication of the study in which input of Roche Diabetes Care personnel exceeds that of conventional monitoring will be considered as a joint publication by the Investigator and the appropriate Roche Diabetes Care personnel. Authorship will be determined by mutual agreement.

## **13 Clinical Conduct, Study Material and Accountability**

### **13.1 Material and Procedures**

#### **13.1.1 Numbering of Subjects**

As soon as a subject has signed the Informed Consent Form, the Investigator or authorized study staff will allocate a subject ID number via the eCRF-system.

The subject ID number consists of 2 digits for the site and 3 digits for the subject: **SS-XXX**.

#### **13.1.2 Supply of Study Material to Study Sites**

The Investigator will receive all of the materials needed to initiate and conduct the clinical study. The materials include, but are not limited to:

- Study protocol, final approved version.
- Electronic CRF, available on-line.
- Investigator Site File including all relevant documents.
- Study devices (intervention group only):
  - ACCU-CHEK® Connect Diabetes Management System (DMS) and consumables
  - Smartphones, if applicable.
- Sponsor - provided study laptop
  - Subjects Questionnaires.
  - HCP and School Nurse Questionnaires
- Packaging material for return of study devices (interventional group only)
- Central lab kits, (for HbA1c and urine pregnancy) manual and shipping labels and supplies

#### **13.1.3 Dispensing of Study Devices**

The site will be responsible for maintaining a supply inventory log recording receipt and disposition of all the devices with serial or batch numbers and supply materials, if applicable.

For this purpose, a study-specific **Supplies Dispense & Return Form** shall be completed for each subject.

#### **13.1.4 Return of Study Devices**

Subjects will be permitted to keep the dispensed ACCU-CHEK® Aviva Connect Blood Glucose Monitoring System at the end of the study.

Subjects who received a sponsor-provided Smartphone for use during the study must return it at the end of the study.

For this purpose, a study-specific **Supplies Dispense & Return Form** shall be completed for each subject.

Sites will be asked to return the study provided laptop

### **13.1.5 Destruction of Study Devices**

It will be decided if the study devices will be returned to the Sponsor for after-use-inspection.

If devices are not to be returned to the Sponsor, destruction (of used and unused devices including comparative devices) is only allowed upon written permission from the Sponsor.

## **13.2 Site Selection**

Sites will be selected for participation in this clinical study by the Sponsor. These sites must have qualified personnel and must be equipped with the appropriate medical facilities to fulfill the study requirements. The clinical sites must be associated with and under the guidance of an Ethics Committee which satisfies all Regulatory Authority requirements and conducts meetings on a regular basis. These sites must also have an adequate subject population to meet the study requirements.

Sites will include pediatric endocrinologist as well as pediatric diabetes specialists who focus on the management of pediatric type 1 diabetes. All sites will be familiar with diabetes data management software to review patient generated data.

Sites will be approved for participation by the Study Manager.

## **13.3 Responsibilities of the Site Principal Investigator(s)**

The site Principal Investigator(s) shall be responsible for the day-to-day conduct of the clinical study as well as for the safety and well-being of the study subjects.

The site Principal Investigator(s) must satisfy the following requirements:

- Have adequate knowledge and experience in diabetes care management as documented in the Investigator's Curriculum Vitae.
- Have the resources and time to comply with the requirements of this clinical study.
- Have access to an appropriate medical facility and equipment necessary for the conduct of this clinical study.
- Have primary responsibility for the accuracy, legibility and security of all study data.
- Have an adequate subject population to meet the requirements of the study.
- Observe confidentiality at all times throughout the study.
- Ensure only eligible subjects, per the approved study protocol, are enrolled into the study and that written informed consent is obtained from each subject.
- Follow protocol procedures and provide accurate data in a timely manner.

### 13.4 Study Monitoring and Auditing

It is understood that the responsible Roche Diabetes CareMonitor (or designee) will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accord with local requirements. It will be the Monitor's responsibility to review the eCRFs at regular intervals throughout the study, to verify protocol compliance and the completeness, consistency and accuracy of the data being entered. The Monitor should have access to the laboratory test reports and other subject records to verify the entries on the eCRFs. The Investigator (or designee) agrees to cooperate with the Monitor to ensure that any problems detected in the course of these Monitoring Visits are reviewed and resolved.

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

Details about requirements for Source Data Verification (SDV) and other aspects of Monitoring will be described in the Study Handbook.

### 13.5 Clinical Site Visit Schedule

**A Pre-Study Qualification Visit** will be conducted prior to the start of the study to ensure that:

- Study sites and their facilities meet the requirements of the study.

**A Site Initiation Visit** will be conducted prior to the start of the study to ensure:

- Investigator understands and accepts his/her obligations in conducting the clinical study according to the protocol.
- Investigator and study staff have reviewed and understood the study protocol.
- Training regarding study devices and study procedures.

**Regular Monitoring Visits** will take place during the course of the study to ensure:

- Continued acceptability of facilities and oversight of the study by the EC.
- Adherence to protocol and applicable regulation.
- Maintenance of adequate subject records.
- All SAEs/AEs are reported to Sponsor and to responsible authority, as required.
- Verification of source data to eCRFs.

At the study termination, study staff will collect all applicable materials and supplies and return them to the Sponsor. After all study data has been collected and verified and the study database has been locked, a **Close-Out Visit** will occur to:



- Ensure all supplies have been accounted for and documented according to the study protocol and the remaining materials either returned to the Sponsor or distributed to the subjects as outlined in the study protocol.
- Complete all monitoring at the study site and close-out any open data discrepancies.
- Ensure all regulatory documents are on file at the clinical site.
- Review the Investigator's responsibilities after the termination activities have been completed.

### **13.6 Training of Investigators and Study Site Staff**

All Investigators and study staff, authorized to perform study procedures, will receive training on the following aspects of the study:

- Clinical study protocol including:
  - Principles ICH & GCP, Declaration of Helsinki and FDA 21 CFR Parts 11, 50, 54, 56, 803, 812, 814 and 820.30; as applicable, with all local laws and regulations and with the regulatory requirements for source data verification
  - Protocol and study procedures.
  - SAE Reporting procedures including completion of SAE Report Form (eCRF) and/or Malfunction /complaint Reporting procedures
  - Monitoring and Audits.
  - As necessary for compliant study conduct.
- Study devices:
  - ACCU-CHEK® Connect Diabetes Management System (DMS) and consumables
  - Smartphones, if applicable.
- Completion of eCRF:
  - Passwords, Data Entry, Corrections, Query process, and Sign-off.
  - Completion of SAE Report Form and sending to the Sponsor.
  - Documentation of protocol violations and deviations.
  - Device data upload procedures if applicable
- Completion of Subject Questionnaire – electronically by means of provided study laptop (at site) into the study eCRF web based system..
- Completion of HCP Questionnaire – electronically by means of the provided study laptop into the study eCRF web based system .
- Procedures for Central Lab (Handbook etc.)



## 14 Reporting of Protocol Violations and Deviations

For the purpose of this study, the following definitions will be used:

**Protocol Violation:** a violation that may impact subject safety, affect the integrity of study data and/or affect subject's willingness to participate in the study.

**Protocol Deviation:** a violation that does not impact subject safety, compromise the integrity of study data and/or affect subject's willingness to participate in the study.

Protocol violations and deviations will be recorded in the eCRF throughout the study, and documented further via the query-system, as applicable.

The Investigator must notify the Sponsor and the reviewing EC of any protocol violations to protect the life or physical well-being of a subject in an emergency as soon as possible but no later than 5 working days after the emergency occurred.

For protocol deviation, only the Sponsor also needs to be notified.

In this study, visit time windows deviations are not considered as protocol deviations.

## 15 References

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