A Pilot Study to Assess the Effectiveness of Direct to Patient Initiation of CGM in Diabetes

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
BGM	Blood Glucose Meter
CDE	Certified Diabetes Educator
CGM	Continuous Glucose Monitor
DKA	Diabetic Ketoacidosis
HbA1c	Hemoglobin A1c
JCHR	Jaeb Center for Health Research

PROTOCOL SUMMARY

PARTICIPANT AREA	DESCRIPTION
Title	A Pilot Study to Assess the Effectiveness of Direct to Patient Initiation of CGM in Diabetes
Précis	This pilot study will assess whether initiating CGM remotely (outside of the clinic setting) using a CDE trainer can be performed safely and effectively and will test procedures that could be used in a larger, subsequent study.
Devices	Dexcom G6 and Abbott FreeStyle Libre CGM systems
Objectives	To determine whether CGM can be effectively initiated by adults with diabetes with online and remote training instead of clinic-based training
Study Design	Single-arm prospective longitudinal study
Number of Sites	N/A
Endpoint	**Primary Outcome:** Proportion of participants using CGM after 3 months (and at end of study if longer follow up), and frequency of CGM use **Key Safety Outcomes:** Severe hypoglycemia events and diabetic ketoacidosis events **Key Efficacy Outcomes:** Participant-reported outcomes including psychosocial and diabetes treatment satisfaction questionnaires; CGM metrics for hypoglycemia (<54 and <70 mg/dL), hyperglycemia (>180 and >250 mg/dL), time in range (70-180 mg/dL), mean glucose, and glycemic variability (coefficient of variation); HbA1c
Eligibility Criteria	**Inclusion Criteria** • Diagnosis of type 1 diabetes or type 2 diabetes using basal-bolus insulin therapy (pump or injections) • Age ≥18 years old • See a healthcare provider at least once a year • Willing and able to follow the study procedures • Own a smart phone • Understand written and spoken English • Computer access with internet • Resident of U.S. **Exclusion Criteria** • Use of real-time CGM (including Abbott Libre) in last 24 months (interval blinded CGM use is acceptable) • Females that are pregnant, intending to become pregnant, or breastfeeding • Use of MiniMed 670G insulin pump system • Renal dialysis • Plan to participate or participation in a different diabetes management study during the next 3 months

PARTICIPANT AREA	DESCRIPTION
Sample Size and Recruitment	The recruitment target is 30. Enrollment number will not exceed 75.
Intervention	All participants will be asked to use CGM.
Participant Duration	Study participation will be 3 months.
Protocol Overview/Synopsis	Patient Population Adults with type 1 diabetes or type 2 diabetes using basal-bolus insulin therapy who are not CGM users will be enrolled. Recruitment will be through the Wisconsin Research and Education Network (WREN), a network of primary care practices in Wisconsin, or another similar network. Those who indicate that they are interested will be directed to a website with information about the study. If participants have questions about the study, they will be able to request a live chat or phone call to review questions about the study as part of the informed consent process. Individuals interested in participating will be directed to a link on the study website with the IRB-approved electronic consent form for signing. Baseline Data Collection Those who consent to participation will complete web-based questionnaires. Data collected will include demographics, height and weight, socioeconomic status, diabetes history, knowledge and experience with use of diabetes devices, medical history and medications, and health-related physical activity. Questionnaires will collect information related to hypoglycemia awareness, treatment satisfaction, and psychosocial issues. Participant contact information will be collected. Contact information for a diabetes healthcare provider will also be collected. HbA1c After enrollment, the participant will receive a fingerstick HbA1c kit that will be sent to a central lab for measurement. A second test kit will be provided at approximately 12 weeks. CGM Training by Study Team Member Each participant will be assigned a study team member who will be the participant's primary contact and trainer. The study team member is expected to be a CDE. A CDE is a health professional who has experience in diabetes prevention, prediabetes, and diabetes management. The study team member will have received additional training for this study to communicate with the participant about CGM options, teach participants to use CGM, and incorporate CGM into self-management practices.

PARTICIPANT AREA	DESCRIPTION
	Participants will be asked to rate their CDE at the end of the study. Contact between Participants and Study Team Each participant will have scheduled virtual visits with a CDE to learn how to start using the CGM, how to use the data from the CGM, and how to troubleshoot use of the CGM. CDEs will check in with participants weekly during study follow up. Participants will also be able to utilize live chats during training. Live webinars may be available for those who want to learn tips and tricks using CGM. Additional contacts with a CDE may occur as needed. Selection of CGM System Participants will be given information about CGM systems and a recommendation for one of the systems following discussion with the CDE, or an indication that there is no specific recommendation. Participants will have a live chat or videoconference with their CDEs to review the pros/cons of each CGM system before they decide which system they would like to use. After a CGM system is selected, participants will be asked why that system was selected. CGM Initiation A CGM kit will be sent to the participant by mail with a user's manual. Multiple materials will be available for training. The study website will have information and links to online tutorials for initiating CGM (which may include links to YouTube and other websites). A videoconference will be arranged with the participant's CDE to answer questions regarding CGM set up, sensor insertion, alerts and alarms, uploading data, and visualizing data. Participants will be instructed to set up both the CGM receiver/reader and the smart phone app, when applicable. If the participant uses an insulin pump or smart pen, training may include uploading (or linking) of these devices. CGM Data Interpretation Training After the initial onboarding training, participants will use CGM for about 2 weeks before they receive training on how to use data visualization tools and how to use the CGM data to make self-management changes in insulin dosing, meals, exercise, etc. The training approach may vary by participants' age and/or comfort with technology/computers. Decision support tools may be used, if available.

PARTICIPANT AREA	DESCRIPTION
	Changes in Insulin Dosing If the CDE believes that changes in insulin type or dosing that require prescription changes should be considered, this will either be relayed to the participant's primary diabetes care provider or escalated to a nurse practitioner or physician prior to contacting the participant's primary diabetes care provider with the recommendation to implement any such changes. Data Collection and Monitoring The CDE will record all training and participant contacts (including the amount of time involved), and will indicate what approaches seemed to work best for each participant. Additionally, participants will be queried about what aspects of CDE involvement and the provided tools, if any, were useful. CGM data will be regularly uploaded by participants. Participants will be contacted when no data have been received for a week or more. CGM data will be reviewed to identify any major safety concerns with respect to hypoglycemia or hyperglycemia. Questionnaires will be completed on the study website. The occurrence of severe hypoglycemia or DKA will be solicited. Changes in diabetes management will also be recorded. Questionnaires will assess psychosocial issues and diabetes treatment satisfaction. Statistical Analysis The proportion of participants using CGM at 3 months and their frequency of CGM use will be tabulated overall and separately for each CGM system. The data may be assessed by age groups and according to other factors. The frequency of severe hypoglycemia events, hospitalizations, device issues, and DKA events will be tabulated. CGM metrics will be tabulated with comparisons of changes from the first month to the third month. Change in HbA1c from baseline to 3 months will be computed.

SCHEDULE OF STUDY PROCEDURES

	Enrollment	Post-Enrollment	CGM Initiation (Week 0)	CGM Follow Up (Week 2)	CGM Follow Up (Week 4)	CGM Follow Up (Week 8)	CGM Follow Up (Week 12)
ICF • **Eligibility Confirmation**	X						
Baseline Data Collection • **Contact Information** • **Demographics** • **Medical History** • **Questionnaires**	X						
Supply Shipment • **CGM Supplies** • **HbA1c Test Kit**		X					
Follow-Up Data Collection • **Treatment Changes** • **Adverse Event Report**				X	X	X	X
Questionnaires*					X	X	X
HbA1c			X				X
Training with CDE**		CGM Selection	CGM Set up	CGM Data Interpretation	CGM Troubleshooting		
CDE Check-in	*CDE Check-ins will occur weekly throughout the CGM Follow-up Period. Check-ins may be via phone, text or virtual (i.e. Skype)*						

*A questionnaire regarding CGM discontinuation will be elicited at time of discontinuation, when applicable.
**Additional training with a CDE may be completed at interim time points as needed.

Chapter 1: Background Information

1.1 Introduction

A continuous glucose monitor (CGM) measures interstitial glucose concentrations and provides real-time observation of glucose levels, and trend direction. Some CGMs include alarms for when glucose drops to low or high levels. The components of a CGM include a receiver, a transmitter, and a sensor. In December 2016, the FDA expanded the indications for the Dexcom G5 sensor to allow for replacement of fingerstick blood glucose testing for diabetes treatment decisions. Subsequently, in 2018, the Dexcom G6 was approved with factory calibration (i.e., daily calibration with fingerstick blood glucose meter measurements not needed). Similarly, the Abbott FreeStyle Libre was approved as a factory-calibrated sensor for non-adjunctive insulin dosing in 2017.

Both the Dexcom and Abbott devices have a sensor that is inserted in the subcutaneous space and measures the interstitial fluid glucose concentration. The Dexcom G6 provides real-time glucose measurements every 5 minutes with alerts for rising or dropping glucose levels and threshold alarms when a preset hyperglycemia or hypoglycemia level is reached. The Abbott FreeStyle Libre, which also has been referred to as flash glucose monitoring, shows glucose levels only when the user passes the receiver over the sensor to transmit the glucose data to the receiver; glucose recordings are every 15 minutes. For purposes of this protocol, 'CGM' will be used to refer to both the Dexcom and Abbott devices.

Several randomized trials have demonstrated the efficacy of CGM in individuals, particularly adults, with T1D or T2D using insulin.(1-5) Among individuals with HbA1c levels above target, improvement has been demonstrated in HbA1c levels and in a reduction in biochemical hypoglycemia. Among individuals with HbA1c levels at or below target, CGM has been demonstrated to reduce biochemical hypoglycemia while at the same time maintaining excellent HbA1c levels better than a control group.(6) Recent studies have demonstrated the benefits of CGM in individuals with T1D or T2D treated with multiple daily injections of insulin.(5, 7-11) These studies not only demonstrated improvement in HbA1c and reduction in hypoglycemia, but also showed that after 6 months, approximately 90% of individuals were using CGM on a daily or near-daily basis.

In the recent studies, CGM users have reported substantial satisfaction with use of the device and improved quality of life (QOL).(5, 7, 9, 11-13)

In the T1D Exchange registry, CGM use (predominately Dexcom) is associated with lower HbA1c levels irrespective of whether a pump or injections is used for insulin delivery. Mean HbA1c was 9.1% in individuals not using a pump or CGM, 8.6% in those using a pump but not a CGM, 7.9% in those using both a pump and CGM, and 8.0% in those using injections and CGM.

The accuracy of current generation CGMs approach that of blood glucose meters. The mean absolute relative difference (MARD), which is a common metric for assessing accuracy when sensor glucose values are compared with reference glucose values, for the current generations of the Dexcom and Abbott sensors is about 10% or lower, which is in about the middle of the range of accuracy of current blood glucose meters.(14, 15). This accuracy is what led the FDA to approve the devices for non-adjunctive use in dosing insulin.

Despite the compelling evidence of the benefits of CGM, only a minority of individuals with T1D use CGM and an even lower percentage with T2D do. In the most recent T1D Exchange registry data, only about 30% of individuals with T1D were using CGM at endocrinology centers with a strong T1D focus. The percentage is almost certainly lower in community endocrinology practices and substantially lower in primary care practices. As a result, new approaches are needed to expand the use of CGM since its use will benefit most users and improve glycemic control and reduce severe hypoglycemia, which will have major public health cost benefits.

Current generation CGMs have been shown to have a good safety profile. As noted above, the degree of satisfaction with CGM use is high and in recent studies about 90% of patients were using CGM on a daily or near-daily basis after 6 months. The ease of insertion, lack of need for calibration or routine blood glucose meter testing, and extension of sensor life up to 10 days have all made the initiation of CGM easier. Thus, the time has come to consider initiation of CGM use as similar to BGM use, which does not require a prescription.

The objective of this study is to evaluate the initiation of CGM at home and integrating CGM into diabetes self-management, outside of the clinic, using remote training methods. This protocol is for a pilot study to test methods for initiating CGM and training on the use of the CGM data in self-management of diabetes.

1.2 Potential Risks and Benefits of Study Participation

1.2.1 Known Potential Risks

The fingerstick to collect the HbA1c sample could cause bruising and/or pain.

There is a small risk of hypoglycemia when using CGM for insulin dosing if the CGM glucose value is substantially higher than the true glucose level. There also is a small risk of hyperglycemia if the CGM glucose is substantially lower than the true glucose. Participants will be instructed to check their blood glucose when symptoms or expectations do not match the CGM reading. Participants will be instructed to check their blood glucose if the CGM has a warm up period.

There is a low risk for developing a local skin infection at the site of the sensor needle placement. Itchiness, redness, bleeding, and bruising at the insertion site may occur as well as local tape allergies.

Sensors may fracture in situ on rare occasions. In the rare instances when this has occurred in the past, consulting physicians and surgeons have recommended not to remove the wire fragment from beneath the skin as long as there are no symptoms of infection or inflammation. In the event that signs and/or symptoms of infection or inflammation arise such as redness, swelling, and pain, subjects should consult with their physician for the best course of action. If there is no portion of the broken sensor wire fragment visible above the skin, attempts to remove it without medical guidance are not advised. Skin reactions at the sensor site will be reported as adverse events if they are classified as severe (the observation is extremely noticeable and bothersome to participant and may indicate infection or risk of infection or potentially life-threatening allergic reaction).

There is a risk of breach of confidentiality and the possibility that completion of questionnaires could make the participant feel uncomfortable. All data will be maintained in a secure database

with restricted access to help assure confidentiality. Participants will not have to complete any questionnaires or provide any data that they are uncomfortable providing.

The study may include other risks that are unknown at this time.

1.2.2 Known Potential Benefits

It is likely that the participants will benefit from using CGM in the study. However, it is possible that participants will not directly benefit from being a part of this study.

1.2.3 Risk Assessment

The protocol risk assessment for this study has been categorized as no greater than minimal risk.

1.3 General Considerations

The study is being conducted in compliance with the ethical principles that have their origin in the Declaration of Helsinki, with the protocol described herein, and with the standards of Good Clinical Practice (GCP).

Chapter 2: Study Protocol and Data Collection

2.1 Participant Recruitment and Informed Consent

Adults with type 1 diabetes or type 2 diabetes using basal-bolus insulin therapy (pump or injections) who are not CGM users will be enrolled. Recruitment will be through the Wisconsin Research and Education Network (WREN), a network of primary care practices in Wisconsin. Other primary care networks may also be identified for recruitment. The recruitment target to complete the study is 30; no more than 20% of the target will be T2D. The total enrollment number will not exceed 75. Eligible participants age ≥18 years will be included without regard to gender, race, or ethnicity.

Individuals who indicate that they are interested will be directed to a website with information about the study and be able to have a live chat or arrange for a phone call to answer questions about the study as part of the informed consent process. Participants who want to participate in the study will sign the IRB-approved electronic consent form. As part of the informed consent process, each participant will be asked to sign an authorization for release of personal information.

2.2 Participant Inclusion and Exclusion Criteria

Individuals must meet all of the following inclusion criteria to be eligible to participate in the study.

- Diagnosis of type 1 diabetes or type 2 diabetes using basal-bolus insulin therapy (pump or injections)
- Age ≥18 years old
- See a healthcare provider at least once a year
- Willing and able to follow the study procedures
- Own a smart phone
- Understand written and spoken English
- Computer access with internet
- Resident of U.S.

Individuals meeting any of the following exclusion criteria at baseline will be excluded from study participation.

- Use of real-time CGM (including Abbott Libre) in last 24 months (interval blinded CGM use is acceptable)
- Females that are pregnant, intending to become pregnant, or breastfeeding during the study
- Use of MiniMed 670G insulin pump system
- Renal dialysis

- Plan to participate or participation in a different diabetes management study during the next 3 months

2.3 Baseline Data Collection

After informed consent is signed, baseline data will be collected, including the following:

- Demographics
- Height and weight
- Socio-economic factors (education, income, insurance)
- Diabetes history, including diabetes duration, prior management, insulin delivery method, meal bolus determination method, prior severe hypoglycemia, prior DKA
- Medical history
- Medications, including medications (nutraceuticals and other substances) other than insulin being used for glycemic control
- Prior CGM experience and knowledge, including why CGM is not used
- Health-related physical activity
- Psychosocial and treatment satisfaction questionnaires (see section 2.10)
- Fingerstick to measure HbA1c
- Name and contact information for healthcare provider for diabetes management

2.3.1 HbA1c

HbA1c will be measured at a central laboratory after study enrollment. A kit, which will include a blood collection tube and shipping materials, will be sent to the participant to obtain a fingerstick blood sample and return the sample to the lab.

2.4 CGM Training by a Study Team Member

Each participant will be assigned a study team member who will be the participant's primary contact and trainer. The study team member is expected to be a CDE. A CDE is a health professional who has experience in diabetes prevention, prediabetes, and diabetes management. The CDEs will be individuals who have received additional training for this study to communicate with the participant about CGM options, teach participants to use CGM, and incorporate CGM into self-management practices.

At the end of the study, the participants will be asked to rate the CDE as well as the materials provided for training.

2.5 CDE Interaction with Study Participant

Throughout the study, the CDE will interact with the participant through texts, emails, phone calls and/or virtual training sessions. All phone calls will be recorded.

Each participant will have scheduled virtual visits with a CDE to select their CGM system, after CGM supplies are received, after 2 weeks of CGM use, and after 4 weeks of CGM use. CDEs will check in with participants weekly during study follow up. Additional CDE contact will be included as needed and may be requested by the participant at any time.

Live webinars may be available for those who want to learn tips and tricks using CGM.

2.6 CGM Systems

Participants will use either the Dexcom G6 CGM or the Abbott FreeStyle Libre. CGM data will be shared with CDEs and study team members.

2.6.1 Selection of CGM System

Participants will be given information about CGM systems and will review the CGM systems with a study team member. A recommendation may be provided for one of the systems based on discussion with the participant, or an indication that there is no specific recommendation.

After a CGM system is selected, the participant will be asked why that system was selected.

2.7 CGM Initiation

A CGM kit will be sent to the participant by mail, with a user's manual. Multiple materials will be available for training, so that training can be more individualized based upon learning preferences. The study website will have information and links to online tutorials for initiating CGM (which may include links to YouTube and other websites). A videoconference will be arranged with the participant's CDE to answer questions regarding CGM set up, sensor insertion, alerts and alarms, uploading data, and visualizing data. Participants will be instructed to set up both the CGM receiver/reader and the smart phone app, when applicable.

If the participant uses an insulin pump or smart pen, training will include uploading (or linking) of these devices.

2.8 CGM Use and Data Interpretation

After the initial onboarding training, participants will use CGM for about 2 weeks before they receive training on how to use data visualization tools and how to use the CGM data to make self-management changes in insulin dosing, meals, exercise, etc. The training approach may vary by participants' age and/or comfort with technology/computers.

Decision support tools may be used, if available.

2.8.1 Insulin Dose Changes

If the CDE believes that changes in insulin type or dosing should be considered, this will either be relayed to the participant's primary diabetes care provider or escalated to a nurse practitioner or physician prior to contacting the participant's primary diabetes care provider with the recommendation to implement any such changes.

2.9 Follow-up Data Collection

Data will be collected throughout study follow up and will include changes in diabetes management, adverse event and device issues, questionnaires, upload of device data, and HbA1c measurement.

2.9.1 HbA1c

HbA1c will be measured at a central laboratory at 3 months. A kit, which will include a blood collection tube and shipping materials, will be sent to the participant to obtain a fingerstick blood sample and return the sample to the lab.

2.9.2 Device Data Uploads

Instructions for device downloads and device data sharing will be reviewed with each participant as part of their training.

2.10 Questionnaires

Questionnaires are completed by all participants on the study website. Each questionnaire is described briefly below. The procedures for administration are described in the study procedures manual.

MEASURE	CONSTRUCT MEASURED/RELEVANT POINTS
CGM Self Efficacy	15-item measure that evaluates the extent to which CGM users have confidence in their ability to optimally use CGM; 4 minutes to complete.
Diabetes Distress Scale (Management Distress Items)	4-item management burden scale to measures the degree of distress related to diabetes; 2 minutes to complete.
Glucose Monitoring Satisfaction	15-item survey to evaluate treatment satisfaction/burden; 4 minutes to complete.
Hypoglycemia Confidence	Evaluates 8 different common situations where hypoglycemia occurs and evaluates level of confidence of how it can be managed in those situations; 4 minutes to complete.
Clarke Hypoglycemia Unawareness	8-item survey to evaluate experience of symptoms during low glucose events; 4 minutes to complete.
Diabetes Technology Attitudes	5-item survey to measure perceptions about the benefits of diabetes technology and devices; 2 minutes to complete.
Benefits and Barriers of CGM	16 items per section with 2 sections that list situations (e.g., able to share data, glycemic events, physical activity) and designation of whether they are barriers or benefits; 4 minutes to complete.
CGM Discontinuation	3-item survey; participants who discontinue CGM will be asked to complete this.

At the end of the study, participants will complete a questionnaire and/or interview to provide input regarding their participation experience.

Chapter 3: Miscellaneous Considerations

3.1 Adverse Events and Device Issues

Each month, participants will receive an email or text prompt to ask if there have been any adverse events. For each event reported, the participant will be asked if the event could have been related to the use of CGM.

If there is no response, the participant will be contacted again until the questionnaire is completed or the participant indicates that he/she is withdrawing from the study.

Participants will be asked to report the following events:

- Severe hypoglycemia
  - Reportable events will be defined as hypoglycemia in which the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/her needs, was incoherent, disoriented, and/or combative, or experienced seizure or loss of consciousness.
- DKA
  - The participant will be questioned as to whether he/she was seen at a health care facility and/or hospitalized and what the ketone level was if known.
- Hospitalizations

Participants will also be asked to report CGM-related device issues monthly.

3.2 Study Costs

CGM supplies needed during the study will be provided. Participants will be able to keep the CGM after follow up has ended.

Costs of standard medical care for diabetes, including insulin, that would occur even if the participant were not in this study, will be the participant's responsibility.

3.3 Participant Compensation

Participant compensation will be specified in the informed consent form.

3.4 Participant Withdrawal

Participation in the study is voluntary, and a participant may withdraw at any time. The reason for withdrawal will be collected. Additionally, at the time of withdrawal, the participant will be asked to complete device downloads and questionnaires described for the 3-month follow-up time point.

Data for participants who withdraw will be used up until the time of withdrawal.

3.4.1 Pregnancy

If pregnancy occurs, the participant will be withdrawn from the study.

3.5 Contact Information Provided to the Coordinating Center

Contact information for each participant, including name, email address, mobile number, and mailing address will be provided to the JCHR coordinating center. Permission to obtain such information will be included in the Informed Consent Form. The contact information for the study will be maintained in a secure database and will be maintained separately from study data.

Contact information is necessary for shipment of study supplies and for set up of certain apps needed for the study on the participant's personal smartphone. Contact information will be used by study staff including CDEs for training and follow up. Participants will receive reminders via text, email or phone to complete questionnaires or submit study data.

Communications will be provided to a health care provider designated by the participant.

3.6 Confidentiality

For security purposes, participants will be assigned an identifier that will be used instead of their name. Protected health information gathered for this study will be shared with the JCHR coordinating center in Tampa, FL, study team members involved with participant training and review of CGM data, participating institutions and investigators in the research study, and parties involved in collecting and processing of data in accordance with the terms of the study contracts. Participant calls with CDEs will be recorded. Data from participants' personal diabetes care devices and the study devices may be uploaded to Tidepool. Date of birth and email address may be required for creating an account in Dexcom Clarity or LibreView. This information will be accessible to Dexcom and Abbott. If participants do not want to provide their email or do not have an email address then an email account will be created for them.

No identifiable health information of an enrolled participant will be released by the coordinating center, except as described above.

3.7 Quality Assurance and Monitoring

Designated personnel from the coordinating center will be responsible for maintaining quality assurance (QA) and quality control (QC) systems to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

Chapter 4: Statistical Considerations

4.1 Sample Size

The sample size is a feasibility sample and is not based on statistical principles.

4.2 Analysis Plan

The primary purpose of the study is feasibility. Data collected from devices and solicited from participants will be tabulated. Tabulations will include the following aspects:

- Baseline characteristics
- Summary statistics for CGM metrics
- HbA1c
- Occurrence of severe hypoglycemia, DKA, and hospitalizations
- Device issues
- Amount of data captured compared with maximum amount possible
- Questionnaire data

Chapter 5: References

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