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TITLE:

Digital Home-Monitoring of Patients After Kidney Transplantation: The MACCS Platform

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eHealth, mHealth, telemedicine, kidney transplant, remote vital signs, adherence, video consultation

SUMMARY:

The MACCS platform is a comprehensive telemedicine concept aiming at better outcomes after kidney transplantation by sharing key medical information between patients and physicians. A telemedicine team reviews incoming data to detect potential complications and to improve adherence in kidney transplant recipients to achieve better long-term outcomes.

ABSTRACT:

The MACCS (Medical Assistant for Chronic Care Service) platform enables secure sharing of key medical information between patients after kidney transplantation and physicians. Patients provide information such as vital signs, well-being, and medication intake via smartphone apps. The information is transferred directly into a database and electronic health record at the kidney transplant center, which is used for routine patient care and research. Physicians can send an updated medication plan and laboratory data directly to the patient app via this secure platform. Other features of the app are medical messages and video consultations. Consequently, the patient is better-informed, and self-management is facilitated. In addition, the transplant center and the patient's local nephrologist automatically exchange notes, medical reports, laboratory values, and medication data via the platform. A telemedicine team reviews all incoming data on a dashboard and takes action, if necessary. Tools to identify patients at risk for complications are under development. The platform exchanges data via a standardized secure interface (Health Level 7 (HL7), Fast Healthcare Interoperability Resources (FHIR)). The standardized data exchange based on HL7 FHIR guarantees interoperability with other eHealth solutions and allows rapid scalability to other chronic diseases. The underlying data protection concept is in concordance with the latest European General Data Protection Regulation. Enrollment started in February 2020, and 131 kidney transplant recipients are actively participating as of July 2020. Two large German health insurance companies are currently funding the telemedicine services of the project. The deployment for other chronic kidney diseases and solid organ transplant recipients is planned. In conclusion, the platform is designed to enable home monitoring and automatic data exchange, empower patients, reduce hospitalizations, and improve adherence, and outcomes after kidney transplantation.

INTRODUCTION:

Kidney transplantation is the treatment of choice for patients with end-stage renal disease (ESRD) as it prolongs life, improves quality of life (QoL), and saves money and resources compared to maintenance dialysis^{1,2}. QoL is defined as the general well-being of individuals, and health-related QoL (HRQoL) is an assessment of how the individual's well-being may be affected over time by a disease, disability, or disorder³. Recently, QoL, HRQoL, and specific patient-reported outcomes were considered core outcome domains for kidney transplantation, which have become critically

important to patients, health professionals, and regulatory agencies^{4,5}. Kidney transplant recipients (KTR) must change their lifestyle after transplantation, adhere to a complex medication schedule, and perform regular self-assessments⁶. The regular intake of immunosuppressive therapy is of utmost importance to ensure adequate drug blood levels⁷. Extremely low blood concentrations may result in under-immunosuppression, increasing the risk for rejection or the development of donor-specific antibodies (DSA). Acute rejections and DSA are major causes for graft loss. Extremely high blood concentrations of immunosuppressants may result in over-immunosuppression increasing the risk for drug-related side effects, infections, and malignancies. Therefore, strict adherence and regular control of laboratory values is necessary to adjust immunosuppressive therapy within a narrow therapeutic range.

Other frequent complications of immunosuppressive drugs include diabetes and hypertension, which can lead to costly hospitalizations and reduced QoL. To achieve better transplant survival, close monitoring and adherence are essential. Studies in the general population suggest that only ~50% of patients in the Western world are fully adherent to their medication schedule⁸. It has been suggested that approximately 20%–30% of graft losses in KTR are linked to non-adherence^{9,10}. There are many reasons for non-adherence including insufficient communication, misunderstanding, and forgetfulness¹¹. Key pillars for better adherence are good and clear communication and an unambiguous written medication plan¹⁰. Other important factors for adherence are an individually adapted explanation of the therapeutic concept and the understanding of medication and disease. Patient empowerment, which enables patients to better take care of their health, is the basis for better adherence and behavioral changes¹². Being adherent to medication and to a self-assessment plan is crucial for long-term success after kidney transplantation¹³.

The kidney transplant center at Charité cares for KTR from the metropolitan area of Berlin and Brandenburg. Many patients travel several hours for a consultation. Long travel times are an important problem in the care of KTR¹⁴, especially for elderly and frail patients, and also for those who have to manage a family and are working. Other hurdles are travel costs, inconvenience, and loss of working hours¹⁵. Therefore, the Berlin kidney transplant center and local nephrologists (physicians in private practice) share the care after kidney transplantation, which raises the problem of missing or incomplete information during a consultation. To minimize information loss, automatic and safe exchange of key data is needed¹⁶. However, to date, data have been stored in different data silos with no interoperability. Today, data exchange relies on telephone, letters, fax, or e-mails with limited data protection and is highly dependent on individuals. Thus, loss of information and incomplete data are common problems, and automatic, secure data exchange according to European (EU) General Data Protection Regulation (GDPR) remains a rare exception.

Several eHealth solutions have been suggested to support patients after transplantation to better utilize the potential of digitalization for the healthcare of this vulnerable patient group¹⁷. Early detection of complications allows early intervention by a telemedicine team, resulting in less severe complications, less hospitalizations, or a shorter length of hospital stay, as shown in other telemedicine projects^{18–21}. A high hospitalization rate is observed in the transplant population²².

Approximately one-third of KTR are hospitalized annually with average costs of ~6,600 Euro per hospitalization. As a consequence, telemedicine-driven early interventions offer the opportunity to reduce hospitalizations and, by this means, reduce costs and improve QoL. One interesting target is to improve adherence, e.g., with the help of apps or telemedicine concepts. Due to the permanent availability of apps for smartphones, such apps can be included in interventions that aim to increase adherence. DeVito et al. demonstrated in a randomized controlled trial (RCT) that a user-centered app for lung transplant recipients with regular self-assessments, reminder function, remote vital sign monitoring, and an automatic decision support tool could improve adherence to therapy. But they did not observe significant differences regarding the 12-month hospitalization rate and mortality²³.

Schmid et al. conducted an RCT with a comprehensive telemedicine concept after kidney transplantation. They found a significantly higher adherence rate and a dramatic reduction in hospitalizations and costs^{20,21}. These results were confirmed by Lee et al. who reported significantly lower readmission rates within the first 90 days after liver transplantation than the standard of care with the use of additional telemedicine support through smart tablets¹⁹. Their telemedicine features consisted of using Bluetooth devices to remotely monitor vital signs, drug reminders, regular self-assessments, as well as access to educational sessions, text messaging and video conferencing tools. Better QoL, general health, and physical function were observed in patients in the telemedicine group. Adherence was excellent (86%) with respect to remote vital signs, but was only 45% for messaging or videoconferencing. However, not all studies could demonstrate positive effects of apps or eHealth solutions^{17,19}. Han et al. investigated an app with a medication reminder, intake documentation, and shared laboratory values, which also provided information about immunosuppressive therapy. They did not observe any significant difference in adherence between intervention and control groups in KTR, most likely due to high drop-out rates. In this RCT, only 47% used the app after 1 month; the number dropping to 11.5% after 6 months²⁴.

The secure and interoperable MACCS platform for KTR was developed to address the limitations of current post-transplant care, namely the need for close monitoring, regular self-assessments, decreasing adherence, and loss of information between physicians. The platform enables patients to share vital signs, daily medication intake protocols, blood glucose, messages, and well-being with the transplant center via an app (see the **Table of Materials**). Well-being is captured by a simple question ("how are you feeling today?") and a 5-point Likert scale with different emojis (smileys) reflecting the current mood of the patient. In the transplant center, all data are stored directly in the electronic health record (EHR) called TBase. The EHR is tailored for the needs of transplanted patients, is used for regular post-transplant care, and automatically integrates all relevant data from the hospital, outpatient visits, and transplant-specific data such as donor data, ischemia times, and human leukocyte antigen mismatches. A telemedicine dashboard was implemented in the EHR for an easy review of incoming data by the telemedicine team.

The EHR is connected via a secure HL7 FHIR interface with an FHIR server (platform) outside the firewall of the transplant center, which transfers pseudonymized data from the transplant EHR

(TBase) to the patient app. This allows the transplant center to send secure messages, laboratory data, and medication plans directly to the patient's smartphone. A second app will also be connected to the project server to track the medication intake and allow for an alternative transmission of vital signs and well-being (also depicted by five different emojis). Another important partner in the telemedicine project provides specialized software for local nephrologists and has a market share of ~65% in Germany (see the **Table of Materials**). The software connects to the HL7 FHIR server and allows direct communication between the transplant center and local nephrologists. The shared data include laboratory values, medical letters, test results, vital signs, and medication plans. With the use of an automatic data exchange, the platform aims to eliminate loss of information, as well as manual, incomplete, insecure, or late data transmission. By this means, workload is reduced, and time-consuming tasks and errors are eliminated to create significant efficiency gains. The platform also facilitates communication between physicians through an easy exchange of notes to prevent information gaps. Another advantage is the fact that data are transmitted directly into the software of the physicians to be used for daily routine. Thus, physicians only work with familiar software and do not need to use different software tools (**Figure 1**).

The concept of the project is GDPR-compliant, and all of the data are protected according to the highest European standards. Individual data are visible for approved medical personnel only. All information is encrypted and transferred according to HL7 FHIR standards. The patient can give and deny access rights to other physicians through the app and can cancel participation at any time. Data are transmitted only after written informed consent and after a complex onboarding process (digital inclusion process). It is important to mention that all services of the platform are offered as an additional service to patients, free of charge. Thus, patients can choose between regular care or regular care plus telemedicine services. The project started to enroll patients in February 2020, and the additional telemedicine services are supported by two large health insurance companies.

In summary, a comprehensive telemedicine platform for KTR was established. Initially, the German Federal Ministry of Economy and Energy (BMWi) funded the project as part of the open call "Smart Service World" to stimulate the growing number of smart services in healthcare. The basic concept is similar to other comprehensive telemedicine systems^{18,19,23,25,26}. Compared to most telemedicine concepts, the advantages of the platform include its interoperability through standardized HL7 FHIR interfaces and GDPR compliance. The platform has no specific hardware requirements. The apps are free of charge and allow straightforward and easy use. The possibility for an easy multi-channel communication with the telemedicine team might also increase the use of the app for home monitoring. Patients use their regular scale and blood pressure device at home, and no costly and complicated Bluetooth devices are needed. Another innovative feature of the platform is the direct involvement of local nephrologists. Patients are usually treated by a combination of tertiary kidney transplant centers and local nephrologists, who already know the patient from dialysis or predialysis times.

As patients frequently visit their local nephrologists, a comprehensive platform for KTR should also automatically incorporate the local nephrologists to prevent information gaps. Importantly,

the platform also implements automatic safe data exchange and communication with local nephrologists, who can use their regular software and have a direct added benefit due to automatic data exchange with the transplant center. In contrast to similar eHealth solutions, the platform is fully integrated into the workflow of the transplant center and the local nephrologist. The platform also fully integrates the local nephrologist in the data exchange of key variables and provides extensive, safe, and easy communication tools for physicians and patients. The direct benefits for users should increase acceptance and reinforce regular use. Further improvements of the platform are under development, and after establishment of an advanced stable platform, a prospective RCT on KTR is planned to provide solid evidence for better outcomes and cost effectiveness.

PROTOCOL:

The protocol follows the current guidelines of the ethics and data protection committees at Charité - Universitätsmedizin Berlin and is in compliance with current EU GDPR.

1. Perspective of the telemedicine team

1.1. Screening for patients

NOTE: Key data of the project are provided in **Table 1**.

1.1.1. Ask the nurse to screen incoming outpatients or patients on the ward for eligibility. Ask the telemedicine team (nurse and physician) to talk to patients in the outpatient clinic or on the ward about the content, data protection, and aim of the project.

1.1.2. After agreeing, ensure that the patients provide written consent. Ensure that the nurse documents refusals and reasons for not participating and checks again with patients who need time for consideration.

1.2. Role of the nurse in the patient onboarding process

1.2.1. Ask the patient to show his/her smartphone and support the patient in downloading the app from Apple Store or Play Store.

NOTE: If the patient does not own an adequate smartphone, the telemedicine team provides a smartphone for the time of participation.

1.2.2. Search for the patient in the transplant database (TBase).

1.2.2.1. Click on the **Onboarding into MACCS project** button. Ensure that the patient registers on the registration web page with the initial login data automatically created by the transplant database.

1.2.2.2. Ask the patient to create new login data and digitally confirm consent when

redirected to the consent page. Ensure that the patient logs out of the registration page after the platform establishes a safe connection between the patient app and transplant EHR (TBase).

1.3. Patient training by the nurse

1.3.1. Show where to find laboratory values and how these are presented; how to find the text messaging function and how to send a message; how to start a video consultation; how to find a medication plan and how to confirm medication intake; and check the current medication plan for correctness.

NOTE: The current medication plan is transferred to the app automatically once the connection is established.

1.3.2. Demonstrate how to submit vital signs, blood sugar, well-being status, and confirm or decline medication intake. Train the patient how to take the immunosuppressive drugs correctly, and how to measure the heart rate and blood pressure correctly.

1.3.3. Set the patient's current body weight in the telemedicine dashboard by clicking on the **Therapeutic Plan** button, fill in **Weight** in kg, and click on **Confirm Data**.

1.3.4. Define the therapeutic plan for home measurements with the patient and fill out the **Frequency** table in TBase.

NOTE: The individual adherence plan is one part of adherence calculation and is documented in the dashboard.

1.3.5. Discuss with the patients when to contact them in to remind them to forward data; encourage the patients to always call in case of medical or technical problems. Explain the working hours of the telemedicine team, morning hotline for urgent issues, and what to do in case of medical problems or emergencies during and after the regular working hours of the telemedicine team.

1.3.6. Check whether data have been received the next day, and call patients to explain that the data have arrived and ask about any technical issues they may have faced.

1.4. Daily routine of the telemedicine team

NOTE: Monday to Friday from 8 a.m. to 4 p.m. (**Table 2**). Outside regular working hours, the nephrologist-on-call has full access to the transplant database and the telemedicine dashboard. The telemedicine team consists of at least one experienced nurse for every 300 patients, and at least one experienced medical doctor for every 600 patients. One medical doctor is always on duty (**Table 1**). Currently, the telemedicine team consists of two nurses, three junior physicians, and four senior nephrologists.

1.4.1. Daily routine of the nurses

1.4.1.1. Start the day with a structured process in reviewing incoming vital signs in the telemedicine dashboard (**Table 3**). Filter patients according to their critical values as defined in **Table 4** and, if necessary, call the patient or discuss the case with a physician from the telemedicine team.

1.4.1.2. Review well-being data. Call patients if the well-being score is low or if it decreases by more than 2 points. Consult a physician of the telemedicine team if the reason for the decrease in well-being is critical. Review less critical, but suspicious values and, if necessary, discuss these cases with a physician from the telemedicine team.

1.4.1.3. Control incoming medical messages and take action, if necessary. Document all calls and activities in the telemedicine dashboard chart.

1.4.1.4. Identify patients who did not document data in the app as previously agreed. Call the patients and ask about potential technical problems as the reason for the missing data. If technical data transmission is working, remind the patient to regularly forward data as agreed.

1.4.1.5. Answer incoming calls (on medical and technical questions) from patients and local nephrologists. Ask patients at regular intervals about satisfaction with the telemedicine service and usability of the app, and document this information, which is forwarded to the development team for evaluation and continuous improvement.

1.4.2. Routine of the physicians on duty in the telemedicine center

1.4.2.1. Review reports from the nurses on critical values, e.g., high blood pressure (acute onset or over longer periods). Contact the senior nephrologist of the transplant team, or the physician who saw the patient during the last inpatient stay in severe cases.

1.4.2.2. Call the patient, take medical history, and give advice, e.g., how to measure the blood pressure correctly or advise on other medical problems. Follow the patient closely over the next days if a change of medication or an unclear situation has occurred.

1.4.2.3. In severe cases, advise the patient to contact the local nephrologist for a visit, to go to the next emergency room, or to come to the kidney transplant center for follow-up.

1.4.2.4. Contact the local nephrologist or emergency room upfront, if needed. Update the senior nephrologist at regular intervals and have a daily brief consultation with the team in the kidney transplant center on problematic cases. Document all contacts and activities in the telemedicine dashboard.

NOTE: All physicians and nurses in the regular transplant service have full access to the transplant database, including all data in the telemedicine dashboard.

1.4.2.5. Review reports from the nurse on non-adherent patients, analyze the type of non-adherence, and determine a procedure to improve adherence, together with the regular transplant team or local nephrologist. Aim to strengthen adherence through advice and telephone calls or video consultations.

1.4.2.6. Contact a psychologist for behavior therapy to strengthen adherence, if necessary. Follow patients with documented non-adherence more closely. Provide regular feedback to the senior nephrologist and development team.

2. Perspective of local nephrologists

2.1. Training of local nephrologists by the telemedicine team

2.1.1. Inform the local nephrologists about the project through letters, events, and congresses and offer central training courses and video courses.

2.1.2. Make an appointment with local nephrologists for a training and onboarding visit. During the visit, explain the project in detail to the physicians and nurses, discuss data protection, and answer questions.

2.1.3. Explain the contract to local nephrologists, who sign the contract with the transplant center with specified terms and conditions. Explain the technical onboarding process in detail, and provide assistance and documents on how to include patients in the project.

2.2. Onboarding process of patients by local nephrologists using the software system (Table of Materials)

NOTE: Through a general update, all software users have the option to participate, and the current software version has a built-in functionality for a secure connection to the FHIR server.

2.2.1. **Select the patient participant in the software.** Click on the **MACCS** button; after the local software opens an overlay window, click on **Connect**.

NOTE: The local nephrologist can only include patients who are already participating and have gone through the onboarding process at the transplant center.

2.2.2. After the local software generates login data (code and QR code), ask the patients to scan the QR code with their smartphones (or enter the code manually) and complete the onboarding process by clicking on the **Data Sharing** button to indicate agreement.

NOTE: The platform now enables an automatic data exchange of pseudonymized data with the transplant center and the patient app.

2.2.3. Review the data transferred from the transplant center in the local software system.

2.3. Interaction of the local nephrologists with the telemedicine team

2.3.1. Call the telemedicine team if medical or technical problems occur. Ask the transplant center (including the transplant pathologist and senior transplant nephrologist) for telemedicine consultation to discuss the best therapy for the patient, if necessary.

2.3.2. Attend a (virtual) training session, workshop, or onsite presentation.

3. Perspective of patients

3.1 Onboarding process

NOTE: Onboarding of patients will take place with the help of the telemedicine team after explanation of the additional services of the project, data protection, and right to withdraw at any time.

3.1.1 Listen to the telemedicine team and ask questions. Give signed consent and download the app with the help of the nurse.

3.1.2 After receiving the initial login data from the nurse, change the login data, and confirm participation digitally. Enter the new login data into the app and push **Sign in**. After the app opens, enter the well-being status, and click on the **Send** button. Observe the buzzing sound and the confirmation sign (green banner showing **Feedback sent**).

3.1.3. Measure the blood pressure, enter the data into the app, and push the **Send** button. Observe the buzzing sound and the green banner pop-up showing **Vital Data Sent**. Look at the **Show History** list and observe the table with all the values and transmission information.

3.1.4. Open the **Communication** page and send a text message to the nurse. Start a video session by clicking on the **Video** button. Open the **Lab Results** page and look at recent laboratory data. Open the **Medication** page, scroll through the medication plan, and confirm medication intake. Set the alert function for timely medication intake.

3.1.5. After the nurse explains how the medication plan can be forwarded and printed out, log out of the app.

3.2. Use of the app by patients at home

3.2.1. Open the app and enter the vital signs. Look at laboratory values, medication plan, and confirm medication intake.

3.2.2. Send a text message and perform a video consultation. Enter login data in the registration page and look at the consent page, where consent was given for data transfer to the local nephrologist, and where consent can be easily withdrawn.

REPRESENTATIVE RESULTS:

In the first 5 months between February and July 2020, 172 KTR matched the inclusion criteria and were asked to participate (**Table 1**). Out of 172 participants, seven needed to borrow a smartphone (four did not own one, three needed a new one); all other patients owned a smartphone. The app does not need wireless access (Wi-Fi) as data can be transferred by mobile phone via regular telecommunication services, and 2/172 patients were equipped with a subscriber identity module (SIM) card for mobile data transfer. Thirty-three patients (19%) declined for various reasons (**Figure 2**). Some patients did not have Wi-Fi or mobile data and therefore, did not want to participate.

One patient was excluded due to poor cognitive function as they were unable to handle the app. However, one patient with severe visual impairment and one blind patient were successfully enrolled, and five patients participated with the help of their relatives. Two patients participated from abroad, although they do not have easy access to mobile data or Wi-Fi. They transfer data from time to time, when they visit friends with Wi-Fi access or go to Wi-Fi access points in town. In the end, 139 patients were finally enrolled. Of these, 8 patients (5.7%) withdrew, and 131 patients are still participating in the project. The demographic characteristics are shown in **Table 5**, and a first overview of incoming data is depicted in **Table 6**. In total, 29,089 entries were transmitted on 8,954 observation days from 131 active participating KTR, which resulted in 3.4 entries per day and per patient.

FIGURE AND TABLE LEGENDS:

Figure 1: Data flow of the MACCS project. Abbreviations: EHR = electronic health record; MACCS = Medical Assistant for Chronic Care Service.

Figure 2: Screening and drop-outs between February 28, 2020 and July 27, 2020.

Table 1: Key information of the MACCS project. Abbreviations: MACCS = Medical Assistant for Chronic Care Service; KTR = kidney transplant recipients.

Table 2: Core features of telemedically supported case management.

Table 3: Priorization of tasks of telemedicine team and local nephrologists.

Table 4: Assessment of vital signs.

Table 5: Demographic and clinical characteristics of participating patients. Abbreviations: Min = minimum; Max = maximum; ADPKD = autosomal dominant polycystic kidney disease.

Table 6: Number of vital signs received during the observation period.

DISCUSSION:

A comprehensive telemedicine platform was created to improve the care of KTR. The platform was readily accepted by patients with excellent participation in sending vital signs from home. To develop the platform and to provide these services to patients, extensive software engineering was necessary. Critical steps included (a) constant software development with the involvement of all stakeholders from the beginning, and (b) a comprehensive data protection concept, which was achieved with the help of a specialized law firm. This iterative process resulted in the release of several new versions of the different software components and apps, which were engineered toward a more patient-centered design. Key factors for the successful implementation of new features were close communication through weekly meetings, constant troubleshooting, involvement of the users, and quick problem-solving. During the initial development process, several workshops were organized with participation of all user groups (including patients) to find the best software design and to prioritize the most important features for a basic first version of the platform. In these workshops, patient engagement focused on acceptance issues, usability, identification of key features, and patient burden for documentation. Additional interviews with clinicians, local nephrologists, and patients helped to shape the project toward the needs of the different users. An extensive literature search provided additional insights¹⁷.

Interoperability is of crucial importance for future development, acceptance, and scalability. Therefore, the most advanced interoperability standard, namely, HL7 FHIR, was implemented. This allows further development in an open-source environment and the utilization of the large HL7 FHIR community for rapid adaptation of future needs (e.g., to integrate wearables or other apps) and a seamless integration into other eHealth solutions (e.g., EHR of hospitals and health insurance companies, different physicians' software) or a larger eHealth framework (e.g., GEMATIK, the future German patient health record). Another important feature of HL7 FHIR-derived communication is the availability of highest data privacy. An extensive data protection concept was developed based on informed consent and secure data transfer of only pseudonymized data according to strict EU GDPR. Because development of the platform takes place in a separate developer container, and researchers only have access to pseudonymized data on the replication server, regular developers and scientists have no access to the live system with patient data. The partner, who hosts the FHIR server, has access only to pseudonymized patient data. The key for pseudonymization is separated and transferred during the onboarding process to the patient app, where the patient can administer access rights. All servers with patient data are localized within the EU according to the latest GDPR. Thus, patient confidentiality is already protected by virtue of the platform design.

However, an app can only help if it is used, similar to drugs or other interventions in healthcare. Therefore, a simple and intuitive user experience in combination with regular reinforcement, e.g., through the telemedicine team is needed to ensure effective intervention. If patients feel that they benefit directly from the app (e.g., through additional communication services, ease of documentation, reminder function), they will use it more often. In this regard, patient empowerment, flexibility, adjustment to individual needs, and teaching are critical to achieve a

constant and regular use of the app. As a consequence, constant assessment of use, acceptance, and attrition rates as well as a thorough analysis of problems is needed for a steady improvement of the platform to achieve the goal of better patient care. Last, but not least, the successful implementation of the platform relies on the “human factor”, namely, the usability of the system, its effect on the workload, and the interaction of the telemedicine team with the patients as well as their local nephrologists. The platform is one of the first to include local physicians and thus enables a seamless treatment with all information on hand to the treating physician, irrespective of the location. The data exchange between physicians is facilitated by the high interoperability of the HL7 FHIR communication standard. The system allows all physicians to work with their regular software, with no need for additional software and passwords, which is a prerequisite for good acceptance. An extension of the platform to other individual healthcare providers such as pharmacists, physiotherapists, other medical specialties, or hospitals, is a goal for the near future.

Another important aspect was close communication with healthcare providers, who are strongly interested in digital pilot projects, which have the potential to save costs and improve outcomes. Because healthcare providers were part of the initial consortium, those discussions had already taken place in the early stages of the development process. As a consequence, a detailed analysis of healthcare costs after kidney transplantation and potential cost reductions were performed right from the beginning. It showed hospitalizations and premature graft loss, with return to dialysis being the most important cost factor in this patient group. Importantly, both factors also have direct adverse consequences on patients’ QoL. It is obvious that fewer hospitalizations and graft losses are associated with cost reductions and at the same time, directly improve QoL. As non-adherence is an important factor for long-term graft survival, the concept aims to strengthen adherence through multiple ways, e.g., efficient communication, medication reminders, and better self-assessments. Ultimately, all these factors should help to assist in behavioral changes, to better detect health indicators, and empower the patient to better manage the chronic disease. Although educational and behavioral interventions to increase adherence are promising, the effect size seems small²⁷. Thus, multifaceted and individualized interventions for better empowerment of patients are important for better efficacy²⁸ and must eventually be combined with novel eHealth interventions^{17,19,29}. Similar to other comprehensive telemedicine projects^{18,19,21,23,25,26}, this should lead to improved adherence and a more timely detection of adverse events.

As demonstrated by another German group, such a comprehensive telemedicine project is cost-effective, may reduce hospitalizations, and prolong graft survival, and therefore avoid costly dialysis treatment²⁰. The group in Freiburg observed a dramatic 60% reduction in unplanned hospitalizations, resulting in a cost reduction of approximately 5,000 Euros in the first year after transplantation. Even when the authors accounted for the telemedicine costs, they could demonstrate cost savings of approximately 2,000 Euros per patient in the first year after transplantation. These assumptions are currently being evaluated by regular prospective assessments of key performance indicators such as adherence, rejection, development of DSA, graft loss, emergency room visits, and hospitalizations¹⁸. Based on the convincing evidence from other studies^{18–21}, two large German health insurance companies decided to support the MACCS project. Hopefully, more insurance companies will participate in the future. Ultimately, a

prospective randomized trial is needed to demonstrate the effect of the telemedicine concept on patient adherence, QoL, hospitalizations, cost reductions, and long-term outcome.

A potential limitation is the fact that the platform depends on the willingness of the participants to regularly use the apps and ultimately integrate the apps into their daily routine. To achieve high acceptance, extensive educational sessions were established during the onboarding process, and new participants were called on the day after inclusion. Technical support is provided by the telemedicine team to patients who are not familiar with apps. Another limitation is the fact that the system relies on manual patient data entry, with the potential for typing errors. Patients may also get annoyed by having to repeatedly enter data into the app. Automatic data entry of vital signs with Bluetooth devices would improve data quality and comfort but adds complexity and costs. In the first version of the platform, complexity and costs were reduced by utilizing the patient's own scale and blood pressure devices. In addition, the app was optimized for flexible manual data entry. Another inherent limitation is the fact that data entry of the patients has to be trusted, in particular, regarding the intake of their medication. However, the precise evaluation of true adherence is difficult, and concepts for adherence measurements, which rely on more technical solutions, are not yet standard.

In the future, it is planned to incorporate Bluetooth Internet of Things (IoT) devices for automatic and more precise data transfer. An interesting option to improve adherence is a Bluetooth-connected pillbox, which tracks the opening of a pillbox, but does not track the actual swallowing of a pill. Thus, similar to self-reporting, there is still uncertainty with regard to medication intake³⁰. It is also possible to directly track swallowed pills, which are attached to a sensor. After activation in the stomach, the sensor transmits a signal to a smartphone via a patch attached to the belly. However, as the use of the patch was associated with discomfort, further research is needed to develop the system for routine care^{31,32}. At the end of the day, patients are responsible for their actions. The goal is not to perfectly track non-adherence, but instead to assist and empower patients for better adherence. The platform provides drug reminders, easy communication tools, information on the latest medication plan, laboratory values on the smartphone, a helpline, and a telemedicine team, and thereby creates an environment for maximal assistance to fulfill the tasks for optimal outcomes.

In the first version of the platform, the most important features, which were defined and prioritized with all stakeholders during a design and development process, were implemented. The focus was to incorporate features with a proven impact on adherence as well as those with high feasibility and medical relevance (e.g., medication reminder, medical messages, medication plan, laboratory values of highest interest). In addition, for automatic data transfer, the main pillar for successful implementation of such a transfer is the "human factor", namely, a competent telemedicine team, which has to train, support, and communicate with patients and local nephrologists. The constant communication with the telemedicine team motivates patients to stay in the project. To deal with all the incoming data and the high information load, the team developed a strictly structured daily schedule, focusing on the most urgent problems first. Furthermore, the telemedicine team is in close contact with the regular medical team involved in post-transplant care for an integrated care. Steady improvement of the telemedicine features

with stepwise implementation of new features, according to the needs of the participants, is planned. Therefore, regular assessments of satisfaction and problems are of utmost importance, to define areas that need improvement.

As a next step during the current COVID-19 pandemic, a full integration of video consultations is planned. In a further step, a platform for educational purposes will be created, which can provide important content regarding transplantation and immunosuppression to patients in an easily accessible way. Other planned features for the patients are a better graphic display of vital signs and adherence as well as simple statistics for concise information and better illustration. In addition, expansion to other software systems to integrate other nephrologists and general practitioners is planned. The development of secure, web-based access would allow physicians to get access to patient data. Such web-based access could also serve as an emergency access for physicians to retrieve medical history and medical records through a temporarily activated emergency access to the platform. Another long-term goal is the development of a dashboard for antibiotic stewardship for better treatment of frequent urinary tract infections. Currently, a telemedicine unit within Charité is supervising patients and deciding, on a case-by-case basis, when patients reach critical thresholds. The additional workload requires additional manpower. Whether the additional tasks are performed by an increased healthcare team or by a separate telemedicine team is a matter of debate and depends on the local situation. However, extensive daily communication between all involved healthcare professionals and a structured therapeutic approach are essential for uniform and successful treatment.

Communication with patients is time-consuming and creates a high workload and may lead to “information overload”. Thus, communication and the identification of the most critical patients are the bottlenecks in the current approach. The integration of novel artificial intelligence (AI)-driven technologies for automated communication on routine questions and automated detection of the most critical patients would reduce the workload of the telemedicine team and help focus on the most urgent cases. As monitoring is time- and cost-intensive, automated monitoring systems based on complex-event detection modules are key technologies to fuel the healthcare sector productivity in combination with individual risk predictions to focus limited resources on the most vulnerable patients. However, only approved AI components will be implemented after profound evaluation. Using the text interface of the existing patient app, automatic assessment of patient requests is planned so that urgent messages can be processed more quickly by medical staff. Noncritical patient requests as well as reminders and support can be provided by a chatbot component improving clinical workflow. Intelligent apps will be added to the open platform, e.g., for diabetic patients, as post-transplant diabetes is frequent and poor diabetic control affects long-term outcomes. Such apps may give personal advice to patients with regard to food intake and activity.

Another key feature of the platform in the future will be the connection with multiple IoT devices. Automatic data entry from IoT devices and wearables will reduce the burden for the patients to document data daily and will allow for a real-time analysis of patient activity, heart rate, and even electrocardiograms at home. Furthermore, point-of-care measurements with innovative laboratory devices may be added for home monitoring. To handle increased data volumes, Big

Data and AI technologies are needed to detect critical situations, which would optimize the operational workflow of the telemedicine staff and lead to fewer patient constraints. In the end, such real-time analytics of IoT data streams and chat extractions will allow for a true real-time integrated decision making by using all of the data available from the patient (including medical history, patient record, IoT devices, and chat communications) and hence, for more timely identification of critical situations. The extension of the platform with educational content, personalized advice, and real-time information extracted from all available data sources will allow a more fine-grained overview of the patients' situation and automated warnings that will ease the tasks and workload of physicians and also allow for more patient-centered care through 24/7 communication and reminder functions. Such a system is also highly attractive for other conditions. Transferring the concept to other chronically ill patients and their particular requirements is being pursued.

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DISCLOSURES:

The authors have nothing to declare.

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Figure 1

TBase data:

- medication plan
- laboratory values
- medical letters
- medical messages
- video conferences

Dashboard
EHR

Kidney center – TBase



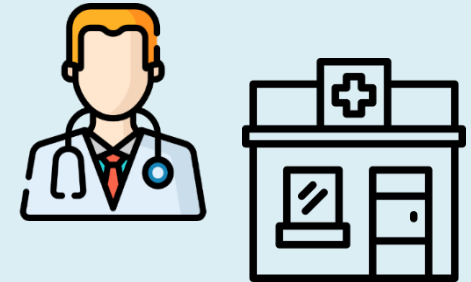
Video conferences

NEPHRO7
EHR

NEPHRO7 data:

- medication plan
- laboratory values
- medical letters
- medical messages
- video conferences

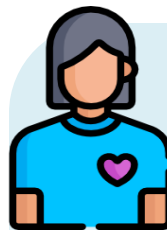
Local nephrologist – NEPHRO7



MACCS
platform
for data exchange



Patient apps:
Comjoodoc EASY
and myTherapy



Patient data:

- medication plan and reminder
- medication intake
- vital signs and well-being
- medical messages
- video conferences

Video conferences

Video conferences

Figure 2

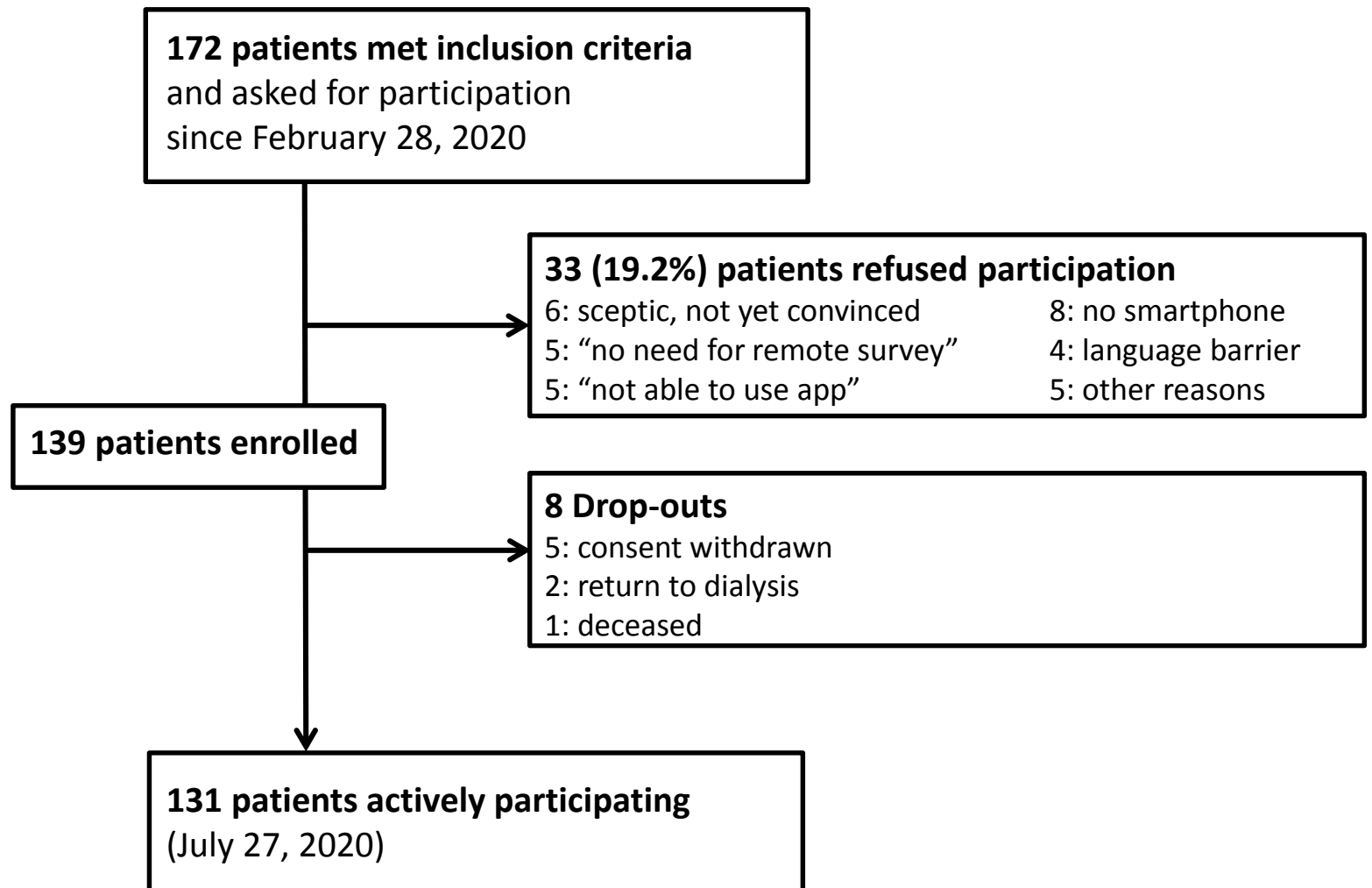


Table 1

Inclusion criteria
Exclusion criteria
Primary outcomes
Secondary outcomes
Role of telemedicine team
Telemedicine team
Expectations on participation

Kidney transplantation and/or pancreas transplantation
Age > 18 years
Cognitive or language barriers
Strengthen the communication between patients and medical professionals to support adherence, reduce hospitalizations, and improve outcomes
Telemedicine team supports adherence and empowerment and aims to detect complications more quickly by regular evaluation of remote vital signs, well-being, sharing of laboratory values and medication plans, medication tracking, and medical support through better communication with a user-centered smartphone app.
Medical experts:
1 physician for 600 patients
1 nurse for 300 patients
Other personnel:
1 assistant (administration)
1 software developer
90% participation in KTR with transplantation less than 1 year ago
Approximately 75% participation in KTR with transplantation less than 1 year ago

Table 2

Telemedicine services, app	Telemedicine team
Any time	8 a.m. – 4 p.m. on working days
Transmission and documentation of vital signs, well-being, blood sugar (for diabetic patients)	Review of vital signs, laboratory values, and well-being on working days
Display of medication plan	Review of medication changes
Display of laboratory values	Medical hotline
Tracking of medication intake	Review of adherence
Reminder of medication intake	Recognition of non-adherence
Messages to transplant center	Intervention and individualized lessons
Video consultations with transplant center	Phone calls and medical messages (questions, problems, assistance, receipts, appointments)
	Video consultations
	Semi-structured onboarding of patients (including technical aspects, education, self-assessment, important symptoms, medication plan, handling of medical emergencies)
	Onboarding of home nephrologists
	Technical support for patients and home
Acute medical problems and symptoms as well as emergency care remain unchanged and are provided by physicians on call, home nephrologists, and emergency rooms.	

Priorization	Nurse ...	Physician ...
1.	reviews critical vital signs	contacts patients with critical values
2.	informs physician on duty	discusses critical cases with transplant team's senior nephrologist
3.	calls critical patients	takes action if needed (e.g., contacts local nephrologist, emergency room)
4.	reviews well-being status	reviews problematic cases with telemedicine nurse
5.	calls patients, if they are not feeling good	reviews cases with transplant team and senior nephrologist
6.	discusses critical patients with physician on duty	reviews incoming messages and laboratory data
7.	reviews less critical vital signs	follows problematic cases
8.	reviews incoming medical messages	answers incoming calls from patients and local nephrologists
9.	reviews patients with missing data	includes data of patients
10.	calls patients, who did not transfer data according to schedule	trains and includes local nephrologists
11.	discusses problematic cases with physician on duty	evaluates project and feedback
12.	reviews normal vital signs	
13.	answers incoming calls from patients and local nephrologists	
14.	identifies potentially eligible patients for onboarding	
15.	includes potentially eligible patients	
16.	evaluates services and feedbacks	
Table 3		

[illegible]

Table 4

	critical	suspicious	normal	suspicious
Systolic blood pressure	<90 mmHg	<100 mmHg	100 - 129 mmHg	130 - 180 mmHg
Diastolic blood pressure	<50 mmHg	50 - 59 mmHg	60 - 89 mmHg	90 - 100 mmHg
Heart rate (beats per min, bpm)	<50	50 - 59	60 - 89	90 - 120
Temperature	<33.5 °C	33.5 - 36.2 °C	36.3 - 37.4 °C	37.5 - 38.0 °C
Change in weight over 1 day	>(-1.5) kg	(-1.5) - (-0.5) kg	± 0.5 kg	0.5 - 1.5 kg
Change in weight over 3 days	>(-2.5) kg	(-2.5) - (-1.0) kg	±1.0 kg	1.0 - 2.5 kg
Change in weight over 8 days	>(-3.0) kg	(-3.0) - (-1.5) kg		1.5 - 3.0 kg
Well-being			1 to 2 points	3 to 4 points

critical
>180 mmHg
>100 mmHg
>120
>38.0 °C
>1.5 kg
>2.5 kg
>3.0 kg
5 points

Table 5

Characteristics	N=131
Age - years	
Mean (Min. - Max.)	50.7 (20 - 83)
Male sex - %	59.5
Transplantation - no. (%)	
1st transplantation	110 (84%)
2nd transplantation	20 (15.3%)
3rd transplantation	1 (0.8%)
Combined pancreas transplantation	5 (3.8)
Days after last kidney transplantation - no.	
Median (Range)	2.249 (29 - 44.039)
Inclusion of de novo kidney transplant patients	
Number	20
Underlying disease - no. (%)	
Glomerulonephritis	62 (47.3)
ADPKD	12 (9.2)
Diabetic nephropathy	7 (5.3)
Alport syndrome	6 (4.6)
Hypertensive nephropathy	5 (3.8)
Other	39 (29.8)

Table 6

Characteristic	N=131
Received vital signs – no.	
Temperature	5,979
Blood pressure	7,656
Blood sugar	1,524
Well-being	761
Weight	5,394
Heart rate	7,775
Sum	29,089
Observation days - no.	
Sum	8,539
Median (Min., Max.)	68 (1 - 150)
Entries per patient and day	3.4

Name of Material/ Equipment	Company	Catalog Number
comjoodoc EASY app	comjoo business solutions GmbH	
HL7 FHIR standard	Medworxs.io	
FHIR server	Medworxs.io	
NEPHRO7	MedVision AG	
myTherapy	smartpatient GmbH	
TBase	Charité - Universitätsmedizin Berlin	

Comments/Description

Patient app for patients to share information with the
transplant center

Provider of MACCS API

Host of MACCS platform

Electronic health record of home nephrologists

Patient app for medication intake and alternative
transmission of vital signs and well being

Electronic health record of outpatient care center at Charité

Dear Vineeta Bajaj,

thank you for giving us the opportunity to revise our manuscript, JoVE61899 "Digital home monitoring of patients after kidney transplantation: The MACCS platform". The revised version has addressed all comments and below we have answered all comments point by point. We are now confident, that the revised version is now acceptable for publication.

Do not hesitate to contact us in case of any further questions

Best regards

Wiebke Duettmann

on behalf of the authors

Editorial comments:

Changes to be made by the Author(s):

1. Please take this opportunity to thoroughly proofread the manuscript to ensure that there are no spelling or grammar issues.

ANSWER: In response to your advice we thoroughly reviewed the manuscript with a native speaker.

2. JoVE policy states that the video narrative is objective and not biased towards a particular product featured in the video. The goal of this policy is to focus on the science rather than to present a technique as an advertisement for a specific item. To this end, we ask that you please reduce the number of instances of "MACCS" within your text. The term may be introduced but please use it infrequently and when directly relevant. Otherwise, please refer to the term using generic language.

ANSWER: In order to comply with the JOVE policy we reduced all product names, e.g. we reduced the term "MACCS" as much as possible (from 50 → 8 times).

3. Abstract; line 69: please explain (briefly) what HL7 FHIR is. Also, please define all abbreviations at first use.

ANSWER: In the revised manuscript, we now defined all abbreviations when we first used is, e.g. we inserted the full explanation for HL7 and FHIR in the abstract and in the introduction (lines 69/70 + 171/172).

4. For in-text formatting, corresponding reference numbers should appear as numbered superscripts after the appropriate statement(s), but before punctuation.

ANSWER: Thank you very much for this information, which we have incorporated throughout the revised version of the manuscript.

5. Please revise the text to avoid the use of any personal pronouns (e.g., "we", "you", "our" etc.).

ANSWER: Thank you for the advice, we changed the text accordingly throughout the revised manuscript.

6. Please adjust the numbering of the Protocol to follow the JoVE Instructions for Authors. For example, 1 should be followed by 1.1 and then 1.1.1 and 1.1.2 if necessary. Please refrain from using bullets or dashes.

ANSWER: In the revised manuscript, we followed these instructions.

7. Please include an ethics statement before the numbered protocol steps, indicating that the protocol follows the guidelines of your institution's human research ethics committee.

ANSWER: We added the sentence "The protocol follows the current guidelines of the ethics and data protection committees at Charité - Universitätsmedizin Berlin and is in compliance with current EU GDPR." See page 5 (line 230-231) at the beginning of the "protocol" chapter.

8. Please ensure that all text in the protocol section is written in the imperative tense as if telling someone how to do the technique (e.g., "Do this," "Ensure that," etc.). The actions should be described in the imperative tense in complete sentences wherever possible. Avoid usage of phrases such as "could be," "should be," and "would be" throughout the Protocol. Any text that cannot be written in the imperative tense may be added as a "Note." However, notes should be concise and used sparingly. You could consider breaking up the protocol into what different teams need to do: telemedicine team, patients, nephrologists etc. and rewrite the protocol for each of these groups.

ANSWER: We reworded all sentences in the protocol section accordingly and changed the text to imperative tense. We also added information on the structured tasks for the telemedicine team, patients and local nephrologists and rewrote the protocol accordingly (including a chapter on the onboarding and structured review process of incoming data, patient requests, and treatment questions).

9. Please note that your protocol will be used to generate the script for the video and must contain everything that you would like shown in the video. Please add more details to your protocol steps. Please ensure you answer the "how" question, i.e., how is the step performed? Alternatively, add references to published material specifying how to perform the protocol action. Please add more specific details (e.g. button clicks for software actions, numerical values for settings, etc) to your protocol steps. There should be enough detail in each step to supplement the actions seen in the video so that viewers can easily replicate the protocol.

ANSWER: We included this information in greater detail in the revised protocol and added screenshots for better understanding.

10. As you have highlighted the onboarding process, will you show how the participation is activated in TBase? Will you be showing how to submit vital signs, medication intake etc.?

ANSWER: We added detailed information on the onboarding process including screenshots and will demonstrate the onboarding in the video.

11. After you revise the protocol, please include a one line space between each protocol step and then highlight up to 3 pages of protocol text for inclusion in the protocol section of the video.

ANSWER: In the revised protocol, we followed the instructions and highlighted the protocol text for the video.

12. Please remove the embedded figure(s) and tables from the manuscript. All figures and tables should be uploaded separately to your Editorial Manager account. Each figure must be accompanied by a title and a description after the Representative Results of the manuscript text. Each table must be accompanied by a title and a description after the Representative Results of the manuscript text.

ANSWER: We removed the embedded tables and figures from the revised manuscript and uploaded them separately to the editorial account.

13. You have some good background information in the Discussion section that would be helpful for the reader to understand if it is moved to the Introduction (e.g., what is a “home nephrologist”, why this project was funded by BMWi, what are the advantages of telemedicine-driven early interventions

ANSWER: We changed the term “home nephrologist” to “local nephrologist”, in order to be clearer for the reader.

As suggested, we moved some sentences from discussion to the introduction:

Line 207 ff: Compared to most telemedicine concepts, advantages: “

Line 127 ff...Early detection of complications allows.....”

Line 204 ff: reason for funding by BMWi: “

Line 213 ff: home nephrologist: “.....Another innovative feature of the platform....”

14. Please ensure that the references appear as the following: [Lastname, F.I., LastName, F.I., LastName, F.I. Article Title. Source. Volume (Issue), FirstPage – LastPage (YEAR).] For more than 6 authors, list only the first author then et al. Please do not abbreviate journal titles and italicize them, not the article title.

ANSWER: We followed these instructions in the revised version of the manuscript

15. Please sort the Materials Table alphabetically by the name of the material.

ANSWER: We corrected the table.

Reviewers' comments:

Reviewer #1:

Manuscript Summary:

With COVID-19 pandemic, need for telemedicine/ virtual medicine has grown. It has also highlighted how important this field is and how much innovation is desired in this area.

Authors share an excellent model they utilized during this time in transplant patients. Their model, protocols and results they share, provides a good insight into the process. I applaud their effort with collaboration from government and health systems to provide better patient care. Patient participation is crucial in telemedicine, as we all have realized in this pandemic.

ANSWER: Thank

Major Concerns:

-Define "well-being" or quality of life outcomes, which authors allude to.

ANSWER: We included both definitions in the revised version of the manuscript:

Line 83 ff: “QoL is defined as general well-being ...”

Line161 ff: “Well-being is captured by a”

- How did the transplant team deal with "too much information/ information overload" from patients

ANSWER: In order to avoid information overload, a well-structured procedure for incoming data was established as outlined in the protocolpage 8 line 285.

In addition, the problem of “information overload” was addressed as potential limitation in the discussion line 589 ff

- We need to highlight-patient confidentiality

ANSWER: According to European GDPR, patient confidentiality is of utmost importance, therefore patient data are protected by highest standards (e.g. HL7 FHIR) and by the privacy by design concept. This problem was highlighted in the introduction (line 171-175, 193-197, 207-208). In addition, a sentence was added to the protocol, that the protocol adheres to current guidelines of Charité data protection committee and GDPR (line 230-232). Finally, we added some sentences to the discussion to highlight the privacy by design features of the platform (line 458-475).

- What is the percentage of population using "smartphones", had access to high-speed wifi and could access apps. Did their education level effect appropriate use of technology.

ANSWER: Thank you for bringing up this important aspect. In order to overcome this issue, we planned right from the beginning to provide smartphones to patients, who do not own an adequate smartphone. Since most patients had an adequate smartphone we only had to lend 7 smartphones. Access to wifi is not crucial as patients can provide data through regular 3G telephone connection. This information was added to the results section. Overall, 95.93% had smartphones and for 7 patients only a smartphone was provided (lines 423ff).

- Were all questions discussed with faculty?

ANSWER: We always discuss upcoming patient requests and treatment related questions in a structured process with the attending transplant physician. For further details see structured process of the telemedicine team line 285ff and table 3)

Minor Concerns:

Grammatical errors. Editing is needed to make it more succinct.

ANSWER: We revised the text critically with a native speaker for grammatical errors.

"on boarding" process- will be better to comprehend if given with sub topics or in bullet points.

ANSWER: Thank you very much for this suggestion. As recommended by the Editor we structured the revised text in numbered sub topics, including the onboarding process, and added more details of the onboarding for a better understanding (line 242-254).

Reviewer #2:

Manuscript Summary:

The manuscript described the development of MACCS ("Medical Assistant for Chronic Care Service") platform that facilitates monitoring, communication between patients and the transplant care team as well as modification to management using a platform aligned with European GDPR for data protection. The execution of these activities currently requires a support team in addition to the primary care team. The authors envision that this platform should help improve patient adherence, decrease health care costs and improve outcomes.

Major Concerns: None.

I would like to congratulate the authors for putting together this impressive program. The manuscript is of interest and summarizes the program as well as the context, advantages and limitations effectively. Some additional clarifications would be of interest:

- Daily routines of the telemedicine team - are there algorithms that the telemedicine follow to ensure consistency in assessment, alerting physicians and modifications in patient management?

ANSWER: Thank you for the comment. In the revised manuscript we provide an extensive overview on the structured review process of the telemedicine team. We added information on this daily routine in the “protocol” (line 285 ff) and added a chapter in line 564 ff.

- References should be provided regarding the "behavioral interventions" by psychologists to promote adherence, and their efficacy.

ANSWER: Thank you for this important point. We critically reviewed and summarized current knowledge the literature in the discussion (lines 506-515):

Lee H, Shin BC, Seo JM. Effectiveness of eHealth interventions for improving medication adherence of organ transplant patients: A systematic review and meta-analysis. PLoS One. 2020 Nov 5;15(11):e0241857.

Pruette CS, Amaral S. Empowering patients to adhere to their treatment regimens: A multifaceted approach. Pediatr Transplant. 2020 Oct 18:e13849.

Tim Mathes, Kirsten Großpietsch, Edmund A M Neugebauer, Dawid Pieper. Interventions to increase adherence in patients taking immunosuppressive drugs after kidney transplantation: a systematic review of controlled trials Syst Rev 2017 Nov 29;6(1):236.

Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, Duvoux C, Jardine AG, Kamar N, Krämer BK, Metselaar HJ, Nevens F, Pirenne J, Rodríguez-Perálvarez ML, Samuel D, Schneeberger S, Serón D, Trunečka P, Tisone G, van Gelder T. Practical Recommendations for Long-term Management of Modifiable Risks in Kidney and Liver Transplant Recipients: A Guidance Report and Clinical Checklist by the Consensus on Managing Modifiable Risk in Transplantation (COMMIT) Group. Transplantation. 2017 Apr;101(4S Suppl 2):S1-S56.

- The authors should describe how inpatient information is linked to outpatient data.

ANSWER: As pointed out in the revised introduction (lines 171- 190) we established a HL7 FHIR interface between the patient app and the EHR in the hospital (TBase), who collects all relevant data from different hospital sources. The hospital EHR (TBase) is also connected via the HL7 FHIR interface with the EHR of local nephrologists in private practice (NEPHRO7 by MedVision AG). For clarification we added figure 1 to depict data flow.

- Table 5: Please clarify "sum" - are you referring to total number of observations per patient?

ANSWER: Sorry for the lack of clarity. In the revised version we clarified that the sum refers to the total number of received vital signs and the total number of observation days, respectively.

- In the Discussion:

o Can the authors elaborate on the process of patient engagement in study design, software development, and interface implementation?

ANSWER: During the public funded project period, we performed several design workshops with all stakeholders, including patient representatives. Patients did not comment on software design and interface implementation but on acceptance issues, usability, identification of key features, and patient burden for documentation. For clarification, we added a sentence in the discussion (line 448-456)

o Given there is involvement of both nephrologists as well as transplant nephrologists from tertiary centers, how does the telemedicine team know who to contact with the results?

ANSWER: The reviewer addresses an important concern, which is solved by a well-structured communication process in the daily telemedicine routine as outlined in the revised protocol. In general, the telemedicine team first approaches the hospital health care team, who has seen the patient during the last visit. If the hospital health care team decides that the local nephrologist should get involved the telemedicine team will contact the local nephrologist.

In the same note, how would the authors plan to promote efficiency in this context as there seems to be quite a bit of redundancy.

ANSWER: As pointed out in the introduction the system can reduce work load due to data transfer (run extra blood values, less notes must be filed..)

Today, loss of information, information gaps, and the need for manual data transmission create a high workload and are largely inefficient. Automatic transfer of data and documents directly to patients and physicians eliminate all these problems and by this means create significant efficiency gains (line 183).

Should there be integration of the health care team in the activities, instead of a telemedicine team?

ANSWER: The close communication between telemedicine team and regular health care team is fundamental for success. The telemedicine team consists of experienced nurses and M.D.s, and - as pointed out in the structured workflow - the team will communicate with the health care team on a daily basis and approach the treating physician in case of problems. In addition, we addressed this important issue in the discussion (line 561-568).

Incorporation of AI and algorithms to alert aberrancies and their handling - would probably relieve burden. Yet, require evaluation of their own.

ANSWER: As pointed out in the revised discussion, the incorporation of AI tools is planned after thorough evaluation (line 591-598).

o If there is already implementation of the program, is it likely that a randomized controlled trial will be done in the future?

ANSWER: Thank you for this comment. Yes, indeed we are planning to perform such trial after the end of the pilot phase, when we have established a stable platform according to the needs of a clinical trial. This was integrated into the text (line 225-227).

Minor Concerns:

The manuscript would benefit from editing for English language and grammar. Below is but a selection of examples:

ANSWER: We revised the manuscript profoundly for language and grammar. We corrected all minor concern points. Thank you very much for your help!

In the body of the manuscript:

- "Kidney transplantation is the method of choice for patients with end-stage renal disease." When stating "method" the authors may refer to "treatment."

Done

- "Too high blood concentrations .." should mention "of immunosuppression"

Done

- "in a narrow and individual range" should read with a narrow therapeutic range

Done

- "distress" - do you mean inconvenience?

Done

- "automatic decision support" should read automated decision support tool

Done

- "This results" should read "these results"

Done

- This understanding - or better called "empowerment"- is the basis for better adherence and a change in behavior

Done

I wonder if the statement would be understood better as follows: "patient empowerment to take charge of their care may be the basis of better adherence and behavior modification.

Done

- 86% adherence to telemedicine is deemed "excellent" - How does that compare to adherence to regular appointments?

ANSWER: This is a good point because the sentence is misleading. 86% adherence regarding the telemedicine functionality "remote vital signs" compared to other telemedicine functionalities such as "response to text messaging [...]" and "use of [...] video messaging" with each 60% and 6%, respectively. The authors did not provide any data on adherence to regular appointments. For clarification, we changed the sentence (line 148-150).

- Does "home nephrologist" mean "Personal nephrologist"?

ANSWER: We changed that term to local nephrologist and explained this term in the introduction (line 115-118).

- "physicians only work in the software"

Physicians work with the software/platforms they are already familiar with.

Done

- "patient-centricity" - could be changed to "patient centered care"

Done

In the protocol:

- semi-structured lesson - does lesson mean "training"?

Done

In the Figure and Table legends, Table 1: Key information 350 of the MACCS platform:

- "Telemedicine team supports adherence and aims to detect complications more timely"

Should say "in a more timely fashion."

Done

- "other personal"

Should be personnel

Done

- "participation in KTR"

Should be "participation of KTR"

Done

Onboarding process of test patient into MACCS platform

Please do not publish these screenshots! They are for a better understanding of the process but, as the platform is still in adaption, can be changed at any time

Regarding screenshots of TBase, another publication is currently submitted to JoVE



Patient: Herr Test patient, Testinchen (01.01.1960) - TBase_CCM



Stammdaten



Fest.Med.Daten



Ärzte



Diagnose



Prozeduren



Verlauf



Labor



Medikation



Untersuchun...



Krankenhaus



Transplantati...



TMZ-Kurve



TMZ-Dashbo...



Patient anmelden



Einwilligung drucken



Abmelden

Informationen

Status: Nicht Eingeschlossen



Patient: Herr Test patient, Testinchen (01.01.1960) - TBase_CCM



Stammdaten



Fest.Med.Daten



Ärzte



Diagnose



Prozeduren



Verlauf



Labor



Medikation



Untersuchun...



Krankenhaus



Transplantati...



TMZ-Kurve



TMZ-Dashbo...



Patient anmelden



Einwilligung drucken



Abmelden

Informationen

Status: Konsent ausstehend

Anmeldedatum: 15.12.2020



Initialer Benutzername: NNvrFd

Initiales Passwort: 3VFGEckS

Registrierungslink: <https://easy.comjoo.com/register/>

Register





 Please register here with the login details that you have received by email. 

* Please enter your temporary username.

* Please enter your temporary password.

Next

 If you have already registered, go to the login page. 
[Go to login page](#)

Register

 Activation —  Set E-Mail —  Verification —  Set Password —  Done

* Submit Email

 testinchen@maccs.de

Next

reset form

Register

Activation — Set E-Mail — Verification — Set Password — Done

* Please assign a new password.

* Repeat New Password

Complete

Manage your consents



You can now log in to the comjoodoc EASY App.

To install the app on your smartphone, follow the corresponding link in the footer.

Nephrologie Charité

Consent granted:

Pending

✓ Accept

✗ Reject

New consent

Insert access granting code

+ Add

Screenshots patient app MACCS project (comjoodoc EASY)

The final design, which we want to
use in the study, has not yet been
completed.

02:33



Health Data



How do you feel today?

Choose status



Very good

Send

Heartrate

Please enter your latest heartrate measurement (Unit: Bpm).

Heartrate

Last submission: 18:13 14.12.2020

[Show history](#)

Send

Blood pressure

Please enter your latest blood pressure measurement (Unit for diastolic and systolic values: mmHg).



Communication



Lab Results



Health Data



Medication

10:46

4G

Heartrate

Last submission: 09:51 16.12.2020

Show history

Send

Blood pressure

Please enter your latest blood pressure measurement
(Unit for diastolic and systolic values: mmHg).

112

78

Last submission: 09:51 16.12.2020

Show history

Send

1

2

3

ABC

DEF

4

5

6

GHI

JKL

MNO

7

8

9

PQRS

TUV

WXYZ

,

0

✕

10:18

4G



Blood pressure

Date	Systolic	Diastolic
16.12.2020 09:51	90 mmHg	60 mmHg
16.12.2020 09:31	112 mmHg	78 mmHg
10.11.2020 19:27	199 mmHg	20 mmHg
05.11.2020 09:22	80 mmHg	30 mmHg

10:42

4G

Medication



For Wednesday, 16. Dec

Morning

[Show Medication](#)

Did you ingest your entire morning-medication?

No ✕

Yes ✓

Noon

[Show Medication](#)

Did you ingest your entire noon-medication?

No ✕

Yes ✓

Evening

[Show Medication](#)

Did you ingest your entire evening-medication?

No ✕

Yes ✓

For the night

No entries



Communication



Lab Results



Health Data



Medication

01:52



Morning

[Hide Medication](#)

Did you ingest your entire morning-medication?

No X

Yes ✓

Bicanorm

Ingredient: Natriumhydrogencarbonat

Dose: 1Tablette

Shape: -

Ingestion: breakfast

Note: -

Ingested?

X

✓

Renagel

Ingredient: Sevelamer

Dose: 2400mg

Shape: -

Ingestion: after breakfast

Note: -

Ingested?

X

✓

Ferrlecit 62,5mg Eurim

Ingredient: Eisen(III)-Ionen

Dose: 1Tablette

Shape: -

Ingestion: before meal

Note: -

Ingested?

X

✓

Amlodipin, Amlo TAD Besilat 5mg

Ingredient: Amlodipin besilat, Amlodipin

Dose: 5mg

Shape: Tabletten

Ingestion: breakfast

Note: -

Ingested?

X

✓

Noon

[Show Medication](#)

Did you ingest your entire noon-medication?

No X

Yes ✓



Communication



Lab Results



Health Data



Medication

10:18

4G

Done

Medikationsplan



Medikationsplan

Seite 1 von 1

 für
 Augustinusklinik
 Charité – Universitätsmedizin Berlin
 Charitéplatz 1, 10117 Berlin

geb. am: Invalid Date

Geschl.: m



Ausgabedruck: 24.09.2020, 10:20

Wirkstoff	Handelsname	Stärke	Form	mg	g	g	g	g	g	Einheit	Hinweise	Grund
Tacrolimus	Corviderm	4 mg/3g	Salbe	1	0	0	0	0	0	g		
Acetylsalicylsäure	Aspirin 500mg	500 mg	Tablette	1x bei Bedarf						St		
Paracetamol	Paracetamol 750mg/12h	0,075 g	Tablette	1x jeden 5. Tag						St		
Chlorhexidin	Luf 100 Balance	900 mg	Flüssigkeit	1	0	0	0	0	0	St	Auf Wunsch des Patienten	
Hydrocortison	Alleson 5 E 500mg	1,4 g	Tablette	0	1	0	2	0	0	St		
Allopurinol	Allopurinol 50mg	0,5 mg	Tablette	0	1	0	0	0	0	St		CTEPH

 Für Informationen zum Inhalt des Medikationsplans und zum Download des Medikationsplans
 siehe Seite 10


10:19

4G

Done

Medikationsplan



Medikationsplan

Seite 1 von 1

für:
ausgedruckt
Charité – U
Charitéplat

Wirkstoff	Handelsname	Stärke
Tacalcitol	Curatoderm	4 %
Acetylsalicylsäure	Aspirin 500mg	500 mg
Fentanyl	Fentanyl AbZ 75µg/63g/h Matrixpflaster	0,1 mg
Johanniskraut-Trochenextrakt (3-6:1)...	Laif 900 Balance	900 mg
~CL~C-Asparaginsäure	Alvesin 5 E 500ml	500 mg
Riociguat	Adempas 0,5mg	0,5 mg

02:33



Nierentransplantation



Tue, 18.08.

H FB hjc

12:15

Fri, 28.08.

Gtrygftgd

08:55

Grytet

09:40

Thu, 03.09.

Trgdrgv

13:07

Mon, 07.09.

Ghugbv

17:08

Waaaasss?

17:10

Wed, 16.09.

G

14:56

Mon, 21.09.

Ufhh

13:00

Gfvh

13:01



10:18

4G

Lab Results



Display by

Report



17.09.2020 08:00

Provided by: Ambulante Nephrologie | Charité —
Universitätsmedizin



18.09.2020 10:30

Provided by: Ambulante Nephrologie | Charité —
Universitätsmedizin



Communication



Lab Results



Health Data



Medication

10:18

4G



18.09.2020 10:30

Provided by: Ambulante Nephrologie | Charité —
Universitätsmedizin

label	Value	Norm	Unit
CREEU	54		mg/dl
U-Glucose (Stix)	28		mg/dl