Universitat Autònoma de Barcelona

IMPROVEMENT IN CLINICAL PRACTICE USING MHEALTH TECHNOLOGY

Mar Gomis-Pastor

THE mHeart STUDY

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DOCTORAL THESIS

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Doctoral Program in Medicine, Departament of Medicine, 2020

UAB

Tesis Directors Maria Antònia Mangues Bafalluy

Maria Eulàlia Roig Minguell *until 02.09.2019*

Academic Tutor Juan Maria Cinca Cuscullola

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Impacto asistencial de la incorporación del mHealth
en la práctica clínica del paciente trasplantado cardíaco

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The developers and funders had no other role in any of the studies or thesis work's design, data collection and analysis, decision to publish, or final preparation of the studies or published manuscripts.

QUOTES FROM THE HEART TRANSPLANT PATIENTS

This thesis work's greatest achievement is to enable the voice of the patient to be heard. Some of the original quotes from heart transplant recipients received via the mHeart platform were:

FMJ. 2016-10-04 ★★★★★

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CBD. 2016-10-23 ★★★★★

Penso que aquesta aplicació ens està donant moltes coses positives, i més amb una persona com tu que ens ajuda moltíssim! És per això que jo també intento col·laborar perquè el sistema funcioni millor. Moltes gràcies.

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CBD. 2017-03-17 ★★★★★

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ABBREVIATIONS

App	Mobile application
ASHP	American Society of Health-System Pharmacists
AST	American Society for Transplantation
AUC	Area Under the ROC Curve
BPS	Board of Pharmacy Specialties
CAV	Cardiac Allograft Vasculopathy
CHA	Complementary Health Approaches
CIM	Chronic Illness Management
CMV	Cytomegalovirus
eHealth	Use of information and communication technologies for health
EHR	Electronic Health Records
ePROM	Electronic Patient-Reported Outcome Measures
FDA	Food and Drug Administration
HL7	High Level-7
HTx	Heart Transplant
IQR	Quartiles 25-50-75
ISHLT	International Society of Heart and Lung Transplantation
LVEF	Left ventricular ejection fraction
M	Mean
ME	Median
MEMS	Electronic monitoring systems
mHealth	Mobile health
mHeart	A mobile health system directed to heart transplant population

MMF	Mycophenolate mofetil
MNA	Medication nonadherence
MPA	Mycophenolic acid
MPS	Mycophenolate sodium
N	Number of cases
pMRCI-S	Patient Medication Regimen Complexity Index Spanish version
pMRCI	Patient Medication Regimen Complexity Index
Post-Tx	Post-transplant period of time
PRO	Patient-Reported Outcomes
PROM	Patient-Reported Outcome Measures
QoL	Quality of Life
RCT	Randomized Controlled Trial
ROC	Receiver-Operator Characteristic (curve analysis)
SD	Standard deviation
UNOS	United Network for Organ Sharing

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ABSTRACT

ABSTRACT

BACKGROUND AND GOALS

Multimorbidity and therapeutic complexity are undermining health outcomes in chronic populations such as the outpatient heart transplant (HTx) recipients. Medication nonadherence may be a consequence of this complexity and is a direct cause of graft loss and death after HTx. Nevertheless, even these are recognized problems in HTx population, little is known about how best to quantify this complexity or the strategies that could reduce its burden.

In the HTx field, it is widely acknowledged that medical providers should not be solely responsible for managing nonadherence to medication and life-style habits or tailoring complex regimens after-transplant. It has been extensively demonstrated that effective interventions to improve medication adherence and lifestyle habits require a proactive interdisciplinary team and integrated care models. Recent innovations in clinical practice through the development and implementation of internet or electronic-based health technologies (eHealth) may lead to many opportunities to implement such chronic care programs in clinical practice.

Based on these strategies, an eHealth holistic behavioral-based intervention model was implemented in a HTx hospital's outpatient clinic to improve clinical care. The software developed to support the intervention, the mHeart® system, is a mobile application complemented by a website. (Appendix 1) This mobile health (mHealth) tool seeks to improve medication safety and efficacy, to enhance patient-providers interactions and to provide comprehensive clinical care. Clinical pharmacists' skills on patient engagement, motivational interviewing and managerial experience were essential to lead the implementation.

The mHeart system included among other important features, electronic patient-reported outcome measures (ePROMs) to assess health domains such as medication nonadherence and patients' experience of their medication

regimen. These electronic measures should help to increase the feasibility of self-reporting and to overcome current in-clinic limitations. Furthermore, patient real-world and in real-time data provided valuable information for health providers to implement early and personalized interventions via mHealth using behavioral change techniques. Nevertheless, the feasibility of the new mHealth clinical pathway and the quality of electronic instruments should be properly validated before expanding its use, and thereafter tested in long-term larger research.

With these relevant issues in mind, 4 sequential phases were implemented and abbreviated as *The mHeart Study*. This thesis is the result of the specific goals of these phases, presented as consecutive studies. The first phase aimed to quantitatively measure therapeutic complexity by using a validated quantitative index and multimorbidity in chronic-stage HTx recipients. An evaluation of the risk factors for higher therapeutic complexity scores and the association between this complexity and clinical variables post-HTx was also performed. Furthermore, this study included a measurement of the patients' beliefs about the post-HTx medication regimen.

Based on the results obtained in the *first study*, strategies were urgently needed to reduce post-HTx complexity. Therefore, the second phase aimed to develop the mHeart software and to implement an eHealth behavioral-based intervention model to provide healthcare to this complex population in the outpatient setting. Consequently, the study describes the implementation of the model, outlines the facilitators and barriers to the use of mHealth, its benefits, and the willingness to use the model reported by potential users.

Once the model and tool were ready to be clinically implemented, the *third study* came to validate the main clinical aim of the mHeart tool, which is to improve medication nonadherence in HTx recipients. With this aim in mind, an exploratory study was established to measure the quality of the psychometric properties of ePROMs, the feasibility of *the mHeart strategy*, and the patient's satisfaction with the mHeart approach. *The mHeart strategy* designed consisted of an intensive follow-up program based on multilevel indivi-

dually-tailored digital interventions aiming to change behavior by a pharmacist using the mHeart technology in an interdisciplinary environment. The mHeart intervention focused on increasing the opportunities for professional-recipient interactions, and to enhance patient self-empowerment.

Based on above-mentioned stages, this thesis work went further including a randomized clinical trial in outpatient HTx population. The main objective of this long-term study was to improve recipients' adherence to immunosuppressive medication, their experience of therapeutic regimens, and to optimize in-clinic healthcare delivery. For this purpose, the intervention consisted of a long-term *mHeart strategy* versus a traditional in-clinic follow-up by a multidisciplinary team

METHODS

The methods of *The mHeart Study* differ among the 4 studies to define the thesis work. All of them were conducted in the outpatient setting of the Heart Transplant Unit of a tertiary university hospital.

The *first study* was a single-center, observational study which included adult HTx recipients in chronic-stage (i.e. >1.5 years from transplant). We assessed multimorbidity (>2 comorbidities) and the patient-Medication Regimen Complexity Index Spanish Version (pMRCI-S) score. We also analyzed the independent predictors of pMRCI-S and the impact of the index score on specific clinical variables.

The *second study* was an interdisciplinary implementation strategy operated by the Pharmacy Department. The mHeart model was settled in 4 stages: (i) design, (ii) development, (iii) interoperability and implementation, (iv) quality, security and legal requirements. A mixed methods design was applied combining literature review, several surveys, interviews and focus groups. The approach design merged engineering and behavioral science. Participants were chronic-stage HTx recipients, patients' associations, providers, stakeholders and diverse experts.

The *third study* was a single-center, prospective, pilot study. All consecutive early-stage recipients (<1.5 years from HTx) were included. The ePROM psychometric properties assessed were validity, reliability, responsiveness, interpretability and burden. ePROMs consisted of the 4-item Morisky-Green-Levine questionnaire and an adapted version of the Haynes-Sackett questionnaire. The Simplified Medication Adherence Questionnaire (SMAQ) was also applied on-site. Three consecutive medication adherence assessments were performed by a transplant pharmacist. To improve adherence to medication rates, *the mHeart strategy* was delivered during a 1-month period. Patient satisfaction was assessed by a semi-quantitative on-line survey at the end of the study.

The *fourth study* was a single-center randomized controlled trial (RCT). Study participants were adult HTx recipients under follow-up in the outpatient clinic owning a mobile device. Chronic-stage recipients (>1.5 years from HTx) were included in the parallel RCT and were randomly assigned 1:1 to the control group or intervention group. Acute-stage recipients (<1.5 years from HTx) were directly offered the same treatment as the intervention group. There were 3 face-to-face, in-clinic visits spread over 12 months: T_0 (baseline visit), T_1 (6 months after inclusion), T_2 (12 months after inclusion). Control group patients received usual care and were asked to attend face-to-face in-clinic interviews with the clinical pharmacist. Acute-stage recipients and the intervention group received an additional *mHeart strategy*.

RESULTS

In the *first study* we included 135 chronic-stage HTx recipients. Comorbidities significantly increased post-HTx [6 (SD3) versus 2 (SD2) *P*-value<.001]. Patients took 12 (SD3) chronic drugs per day, 58% of them were *drugs to treat comorbidities*. The mean *total pMRCI-S score* was 42 (SD11), higher than in several other chronic diseases. The medication category *drugs to treat comorbidities* predicted a higher *total pMRCI-S score* [OR=3.1 (2.8;3.4), *P*-value<.001]. Therapeutic complexity after HTx had an impact on solid

malignancies [OR=1.1 (1.0;1.2), *P*-value=.02] and renal function [OR=-0.8 (-1.2; -0.4), *P*-value<.001].

In the *second study* an interdisciplinary and patient-centered process was vital to obtain a comprehensive mHealth care model. HTx recipients (n=135) included confirmed access to technology (98%) and willingness to be involved in a mHealth approach (98%). The major priorities embraced, based on the stakeholders' agreement [>75%, n=26], were to improve therapy management, patient empowerment and patient-provider interactions. The latter was especially highlighted by the representatives of the patients' associations. Stakeholder's agreement on mHealth barriers, was weak (<75%). It is recommended for future developers to direct efforts to verify the Technical Team experience, to ensure data confidentiality and to overcome workload, digital divide and interoperability. Experts in different fields were essential to fulfill the quality requirements. Likewise, scientific societies and patient's associations points of view reinforced the mHeart content and scalability.

In the *third study*, we included 31 early-stage HTx recipients, with a mean age of 54 (SD12) years, and most of them were men [22 (71%)]. The recipients were taking a mean of 13 (SD4, range 7-18) drugs per day. Thirteen (42%) patients were unaware of the consequences of nonadherence to medications and 12 (39%) were nonadherent to immunosuppressive treatment. The *content validity* measure showed excellent levels of expert panel agreement for both questionnaires (>85%). Expert agreement on the appropriateness of ePROMs versus the on-site PROMs was strong for the Haynes-Sackett [Kappa=0.826, *P*-value<.001] and Morisky-Green-Levine [Kappa=1, *P*-value<.001] questionnaires. SMAQ and Morisky-Green-Levine ePROMs showed similar measurement domains [*convergent validity*, *Phi*=0.6, *P*-value<.001], which, as expected, differed from Haynes-Sackett ePROMs [*divergent validity*, *Phi*=0.3, *P*-value=.12]. *Reliability* assessment revealed a very strong association between ePROM and on-site PROM scores [*Phi*>0.7, *P*-value<.001]. *Reproducibility* was moderate [Haynes-Sackett Kappa=0.6, *P*-value<.002] or poor [Morisky-Green-Levine Kappa=0.3, *P*-value=.11] due to improved medication adherence rates during the test-re-

test period. According to *responsiveness*, the theory-based multifaceted intervention program improved medication adherence by between 16% and 26% [*P*-value<.05]. Burden analysis showed that ePROMs can potentially overcome traditional on-site limitations (e.g. automatic recording of ePROM responses in the hospital information system). Overall patient satisfaction with the mHeart approach was 9 (SD2) (score 0-10). All patients surveyed [29 (100%)] reported they would recommend the mHeart platform to other recipients.

In the *fourth study* a total of 180 HTx recipients were analyzed; of these, 134 were chronic-stage [intervention N=71; control N=63] and 46 were acute-stage recipients. An attrition rate of 4% was observed. The mean follow-up was 1.6 (SD0.6) years. Mean age was 55 (SD14) years; 30% were women. At the end of the study, of 117 patients using mHeart, 86% were engaged with mHeart every day. Patients' experience of therapeutic regimens significantly improved at the end of the study in the intervention versus the control group, this included: degree of inconvenience perceived by the patient related to taking his/her medication as prescribed every day [*P*-value=.002], patient's knowledge of their regimen intakes [*P*-value=.019], drugs names [*P*-value=.006], drugs doses [*P*-value=.030] and drugs indications remembered [*P*-value=.003]. In addition, patient's awareness of the consequences of nonadherence significantly improved in both groups [*P*-value<.01], and the number of adverse effects reported was significantly reduced to 3 (SD2) at the end of the study in all patients and groups [*P*-value=.000].

Nonadherence rate significantly improved a 65% from baseline in the intervention group [OR=2.3 (0.3;19.7), *P*-value=.000], and compared with control group (46% versus 85%) [OR=6.7 (2.9;15.8), *P*-value=.000] according to the SMAQ questionnaire. Because of the possibility of online follow-up, patients' in-clinic appointment needs with the clinical pharmacist and the intensity of the follow-up were significantly reduced in the intervention group (65%) versus the control group (35%) [OR=3.4 (1.7;6.9), *P*-value=.001].

CONCLUSIONS

Therapeutic complexity measured as the *total pMRCI-S score*, was the highest compared with those previously published in chronic diseases and was mainly influenced by a higher count of *drugs to treat comorbidities*. The pMRCI score is a sensitive method that allows identification of the factors determining therapeutic complexity after HTx and selection of strategies to reduce pMRCI-S values.

A holistic mHealth-based intervention model to improve medication management and clinical care in multimorbidity populations with polypharmacy was successfully developed and implemented in the ambulatory setting of HTx population. The factors which were required to be overcome in order for the model to succeed were: data confidentiality, reducing workload and the digital divide, and increasing interoperability among relevant others. The patients confirmed that 98% of them were willing to use the mHeart system.

The mHeart electronic questionnaires (ePROMs) to measure medication adherence met the existing quality standards and successfully identified nonadherent HTx recipients. The exploratory clinical intervention established showed a promising improvement of 30% in medication adherence rates and produced excellent patient satisfaction and usability scores in the acute-stage HTx population. These results support the mHeart mobile widespread use in larger research and usual clinical practice.

The intensive multilevel strategy performed by a clinical pharmacist in an interdisciplinary environment and using the mHeart technology positively impacted on the health outcomes preestablished. First, important weaknesses in patients' experience of therapeutic regimens were improved. Second, chronic-stage HTx recipients' adherence to immunosuppressive medication significantly improved by 65% according to the SMAQ questionnaire. Confirming that the multilevel behavior-based eHealth strategies used are synergistic and enhance the effectiveness of an intervention to improve medication adherence. Finally, *the mHeart strategy* showed statistically significant reductions on the number of patients needing to travel to the clinic for

follow-up appointments with the clinical pharmacist. The mHealth approach will be, therefore, a feasible way to continue providing long-term advanced individually-tailored interventions by health providers to HTx recipients in the at-home setting.

CURRENT AND FUTURE IMPLICATIONS OF THE THESIS

As a consequence of the legacy left behind by many clinical pharmacists since 1967, the patient-centered clinical care remains at the core of the pharmacy practice in the Hospital de la Santa Creu i Sant Pau. Nowadays, the outpatient setting in chronic complex populations is being recognized as critical for health authorities. Among chronic patients, solid organ transplant recipients present a greater risk of multimorbidity and therapeutic complexity. International guidelines demand transplant centers should strive to have a specialty-trained pharmacist as part of its multidisciplinary team to support health providers with therapeutic complexity management. These unique challenges have inspired *The mHeart Study* thesis work, arising from an actual need to continue raising the profile of the clinical pharmacist in the heart transplant field and to ensure a pharmacist in the Spanish transplant centers.

The implementation of *The mHeart Study* by the Pharmacy Department provided an opportunity to make the clinical pharmacy visible to patients, families and institutions. In addition, mHealth practice was an excellent opportunity to expand the benefits of pharmaceutical care in the health care system. The implementation of a behavioral-change technology model targeting the heart transplant population in our center demanded a multidisciplinary approach. The cardiologists, surgeons, specialized nurses, social workers, psychologists, nutritionists, and clinical pharmacists, among other health providers, are nowadays working comprehensively to improve health outcomes in the HTx population of the Hospital de la Santa Creu i Sant Pau.

Innovative research projects on health institutions are typically short-lived practices with a lack of scalability to usual care. This transition was, however, a priority for *The mHeart Study*, based on prior demonstration of enhan-

ced results. In the case of mHeart, the model was extended into clinical practice in January 2019. Nevertheless, the transition from an innovation project to an established practice was particularly challenging: this entailed funding and organization adjustments led by the Pharmacy Department and the Heart Transplant Unit and also required input from patients, other providers and institutions.

The mHeart model implemented in this thesis has been also scaled to the follow-up of other complex populations in the Hospital de la Santa Creu I Sant Pau. New eHealth projects have objectives in common such as the aim to improve clinical practice workflows, the safety and efficacy of therapies, patient involvement in clinical care and patient-provider interactions. Additionally, the mHealth platform created has been used by many other centers to develop their own versions directed at diverse populations.

Therefore, the implications of *The mHeart Study* thesis research and the eHealth model established will be a promising starting point for an already emerging way of providing further assistance to the most complex populations based on eHealth by the Health Systems.

RESUMEN

INTRODUCCIÓN Y OBJETIVOS

La multimorbilidad y complejidad terapéutica pueden comprometer los resultados en salud en poblaciones crónicas de elevada complejidad como son los receptores de un trasplante cardíaco. Bajas cifras de adherencia terapéutica podrían estar relacionadas con dicha complejidad, y resultan ser una causa directa de pérdida del injerto y muerte tras el trasplante. Las creencias negativas del paciente versus su pauta terapéutica pueden estar a su vez afectando a la experiencia del paciente y a la adherencia a las recomendaciones. A pesar de que esta realidad puede ser conocida por los equipos asistenciales, muy poco se sabe en cambio sobre la magnitud real en nuestro entorno, cuáles son los instrumentos apropiados para medir la complejidad de la terapia, así como cuáles son las estrategias más eficientes para reducir el impacto de esta problemática en la supervivencia del paciente trasplantado cardíaco a largo plazo.

En el campo del trasplante es ampliamente reconocido a nivel internacional que los médicos no son los únicos responsables del manejo de la adherencia a la medicación y estilos de vida, así como de la individualización de los complejos regímenes tras el trasplante. Se ha observado que intervenciones eficaces para mejorar la adherencia a la medicación y estilos de vida, requieren de un equipo interdisciplinar y proactivo, además de un modelo de atención integral y centrado en la persona. Además, el reciente interés que despiertan soluciones innovadoras como las estrategias de salud digital (eHealth) pueden facilitar la implementación en la práctica clínica de dichos programas de atención integral a la complejidad.

En base a la problemática y estrategias planteadas, se implementó en el Hospital de la Santa Creu i Sant Pau un innovador modelo con el objetivo de mejorar la práctica clínica de los pacientes trasplantados cardíacos ambulatorios en seguimiento en consultas externas del Hospital. Este nuevo modelo dibuja una innovadora ruta asistencial, diseñada con un carácter holístico y basada en teorías para promover el cambio conductual. El software desar-

rollado como soporte a esta nueva práctica, la plataforma mHeart®, consiste en una aplicación para el móvil y una página web (Apéndice 1). Esta herramienta de salud móvil (mHealth) fue dirigida a mejorar la efectividad y seguridad de la terapia, promover las oportunidades de interacción entre profesionales y pacientes, empoderar a los pacientes, así como ofrecerles una atención integral y multidisciplinar. La combinación de diferentes habilidades de los farmacéuticos clínicos involucrados, incluyendo la aplicación de técnicas conductuales como las entrevista motivacional para facilitar el acercamiento y compromiso del paciente, así como habilidades de gestión de procesos y equipos, fueron esenciales para dirigir la implementación del nuevo modelo.

La plataforma mHeart incluye, entre otras muchas funcionalidades, instrumentos electrónicos de medida de diferentes ámbitos de la salud (ePROMs). Entre ellos destaca en la población trasplantada la importancia del uso de cuestionarios de medida de la adherencia a la medicación. Los instrumentos electrónicos mediante herramientas eHealth deben ayudar a incrementar la viabilidad de las técnicas de reporte del estado de salud del paciente, así como contribuir a sobrellevar las limitaciones actuales asociadas a mediciones presenciales desde las consultas externas de los centros sanitarios. Además, permiten obtener datos en tiempo real y en el entorno habitual del paciente, conllevando una gran oportunidad para los clínicos que persiguen intervenir de forma anticipada e individualizada a través de herramientas de salud digital.

Estas intervenciones basadas en información a tiempo real y en el entorno habitual de la persona, serán a su vez diseñadas mediante técnicas conductuales para motivar al cambio conductual en el paciente y su entorno. No obstante, la viabilidad de nuevas e innovadoras rutas asistenciales que incorporan la salud digital deben ser convenientemente validadas antes de expandir su uso. Su validación en estudios piloto facilitará el éxito de estudios a largo plazo adecuadamente diseñados según las guías internacionales de intervenciones clínicas en salud digital.

Con estos objetivos en mente, se implementaron 4 fases consecutivas abreviadas como el estudio mHeart (*The mHeart Study*). Los objetivos específicos de cada una de las 4 fases dieron lugar a esta tesis doctoral dividida en 4 sub-estudios consecutivos. La primera de las fases fue dirigida a medir cuantitativamente la complejidad terapéutica mediante un índice ampliamente validado en patología crónica y descrito en la literatura, así como la medida de la carga de morbilidad que soportan las personas trasplantadas cardíacas en estadio crónico (>1.5 años desde el trasplante). Además, se llevó a cabo una búsqueda de los factores de riesgo que incrementan la complejidad terapéutica en estos pacientes, así como de las variables clínicas que puedan verse asociadas a dicha complejidad. Este estudio también incluyó un primer acercamiento a cuáles eran las creencias y la experiencia de los pacientes sobre sus regímenes terapéuticos después del trasplante.

En base a los resultados obtenidos en el primer estudio, se confirmó que son necesarias estrategias de forma urgente para mejorar el manejo de la multimorbilidad y reducir la complejidad terapéutica post-trasplante cardíaco. De manera que el objetivo de la segunda fase fue el de desarrollar el software mHeart, así como implementar el nuevo modelo de salud digital basado en intervenciones de cambio conductual para mejorar el manejo del paciente trasplantado cardíaco ambulatorio. Es por lo que el estudio describe las fases de implementación del modelo, destaca cuáles fueron los factores facilitadores para llevarlo acabo y evalúa cuáles fueron las principales barreras, beneficios y predisposición de los futuros usuarios de la tecnología.

Una vez que el nuevo modelo asistencial y la herramienta tecnológica habían sido implementadas, el tercer estudio se llevó a cabo con el objetivo de validar la principal funcionalidad de la herramienta mHeart, que es identificar a los pacientes no adherentes y mejorar las cifras de adherencia terapéutica post-trasplante. Para ello se llevó a cabo un estudio piloto para validar la calidad de los cuestionarios ePROMs de medida de la adherencia al tratamiento utilizados en mHeart mediante criterios de calidad psicométrica difundidos por asociaciones científicas en este ámbito y de acuerdo

con los estándares. Además, se realizó un estudio exploratorio para medir la viabilidad y eficacia de *la estrategia mHeart* en la mejora de la adherencia y la satisfacción del paciente con la nueva estrategia. *La estrategia mHeart* (*the mHeart strategy*) fue diseñada como una intervención clínica multinivel llevada a cabo por una farmacéutica clínica en el seno de un equipo interdisciplinar con el soporte de la salud digital y mediante el empleo de técnicas del cambio conductual.

En base a las estrategias y resultados obtenidos durante las 3 fases anteriores, se quiso ir más allá, incluyendo un ensayo clínico aleatorizado a largo plazo en pacientes trasplantados cardíacos ambulatorios. Los principales objetivos de este estudio fueron mejorar la adherencia de los pacientes a la medicación inmunosupresora y la experiencia de la persona trasplantada versus su tratamiento, así como optimizar la práctica clínica presencial en consultas externas tras el trasplante cardíaco.

MÉTODOS

Los métodos del estudio mHeart difieren en función de cada una de las fases o 4 sub-estudios de esta tesis. Todos ellos fueron diseñados como estudios unicéntricos llevados a cabo en pacientes trasplantados cardíacos en seguimiento ambulatorio por la unidad de trasplante cardíaco de un hospital terciario.

El *primer estudio* fue un estudio observacional que incluyó receptores de un trasplante cardíaco en fase crónica, es decir de más de 1.5 años desde el trasplante. Las variables principales medidas fueron la multimorbilidad (≥2 comorbilidades diferentes al trasplante) y la complejidad terapéutica cuantificada mediante el patient-Medication Regimen Complexity Index Spanish Version (pMRCI-S). Además, se llevó a cabo un análisis de los factores predictores independientes de un mayor nivel de pMRCI-S, así como el impacto de un mayor nivel de pMRCI-S sobre variables clínicas.

En el *segundo estudio* se realizó un estudio de implementación estratégica de un nuevo modelo asistencial del paciente ambulatorio complejo con el

apoyo de la salud digital. El estudio se llevó a cabo en 4 fases incluyendo: (i) diseño del modelo y herramienta de salud digital, (ii) desarrollo tecnológico del software, (iii) interoperabilidad entre sistemas e implementación en el entorno sanitario, (iv) calidad, seguridad y requerimientos legales. Para ello, se aplicó un diseño mixto que comprendía revisión bibliográfica, encuestas, entrevistas y grupos focales. Los participantes del estudio fueron personas trasplantadas en fase crónica, profesionales y dirigentes sanitarios y profesionales con experiencia en el campo de la salud digital. También fue necesaria la intervención de especialistas en diferentes áreas profesionales; legal, protección de datos, propiedad intelectual entre otros.

El *tercer estudio* fue un estudio piloto prospectivo incluyendo pacientes en fase aguda (<1.5 años desde el trasplante). Las propiedades psicométricas de los instrumentos electrónicos (ePROMs) medidas fueron validez, fiabilidad, sensibilidad al cambio, interpretabilidad e impacto en carga. Los ePROMs evaluados fueron el cuestionario de Morisky-Green de 4 ítems y una versión adaptada del test Haynes-Sackett. Además, el cuestionario Simplified Medication Adherence Questionnaire (SMAQ) fue aplicado durante la entrevista presencial. Se llevaron a cabo tres medidas consecutivas de adherencia a la medicación, dos presenciales por una farmacéutica clínica y tres electrónicas a través de mHeart. Para mejorar la adherencia a la medicación, se llevaron a cabo intervenciones basadas en teorías del cambio conductual durante 1 mes. La satisfacción del paciente con el programa se determinó mediante una encuesta online semicuantitativa al final del estudio.

El *cuarto estudio* fue un ensayo clínico prospectivo aleatorizado. Los participantes fueron pacientes adultos en seguimiento ambulatorio en la unidad de trasplante cardíaco. Los pacientes en fase crónica (>1.5 años desde el trasplante) fueron aleatorizados 1:1 a *la estrategia mHeart* o al grupo control. A los pacientes en fase aguda (<1.5 años desde el trasplante) se les ofreció directamente *la estrategia mHeart*. Se llevaron a cabo 3 entrevistas presenciales durante 12 meses de estudio: T_0 (visita inicial), T_1 (6 meses desde la inclusión), T_2 (12 meses desde la inclusión). El grupo control reci-

bió la atención habitual por el equipo de trasplante además de las visitas presenciales con la farmacéutica clínica. Los pacientes en fase aguda y los pacientes del grupo intervención fueron sometidos a la misma práctica que el grupo control además de a *la estrategia mHeart* validada en el estudio piloto, pero en este caso aplicada durante como mínimo 12 meses.

RESULTADOS

En el *primer estudio* de esta tesis se incluyeron 135 pacientes trasplantados cardíacos en fase crónica. El numero de comorbilidades se vio incrementado significativamente en el post-trasplante [6 (SD3)] respecto al pre-trasplante [2 (SD2)] [*P*-valor<.001]. Los pacientes tomaban una media de 12 (SD3) fármacos diferentes al día, el 58% de ellos para tratar las comorbilidades. El nivel de complejidad mediante el *total pMRCI-S* obtuvo una media de 42 (SD11), muy superior al nivel publicado para otras patologías crónicas. Un mayor número de fármacos de la categoría *tratamientos para las comorbilidades* fue predictivo de elevada complejidad terapéutica *total pMRCI-S* [OR=3.1 (2.8;3.4), *P*-valor<.001]. Esta relación no se observó con otras categorías como el *tratamiento inmunosupresor*. Mayores niveles de complejidad terapéutica *total pMRCI-S* se asoció con un mayor riesgo de neoplasias sólidas [OR=1.1 (1.0;1.2), *P*-valor=.02] y peores cifras de función renal [OR=-0.8 (-1.2; -0.4), *P*-valor<.001]. Asociación que solamente se observó para la categoría *tratamientos para las comorbilidades* (*P*-valor<.01) y no para el *tratamiento inmunosupresor* (*P*-valor>.05).

Para llevar a cabo con éxito el *segundo estudio* de implementación de una innovadora ruta asistencial fue indispensable la implicación de un equipo interdisciplinar que pusiera el foco en conseguir un modelo de atención sanitaria integral centrado en el paciente. Los pacientes trasplantados cardíacos incluídos (n=135) confirmaron que tenían acceso a la tecnología (98%) y predisposición a estar envueltos en un seguimiento de salud digital a través del móvil como mHeart (98%). En base al acuerdo de los profesionales participantes [>75%, n=26], las prioridades del modelo mHeart fueron mejorar el manejo de la farmacoterapia, promover el empoderamiento del

paciente y crear más oportunidades de interacción profesional-paciente. Siendo este ultimo punto especialmente destacado por los representantes de asociaciones de pacientes incluidos en el estudio.

El grado de acuerdo en las limitaciones que supone un enfoque de salud móvil en nuestro entorno sanitario fue bajo (<75%). En base a la experiencia adquirida y para futuros desarrollos se recomendaría dirigir esfuerzos a verificar la experiencia y calidad de la empresa desarrolladora, asegurar un correcto tratamiento de datos de los pacientes, así como la interoperabilidad entre los sistemas. Sin olvidar a su vez buscar estrategias para sobrellevar la sobrecarga de trabajo inicial y la posible brecha digital tanto de profesionales como de pacientes. Para asegurar estos requisitos de calidad diferentes expertos fueron involucrados durante todo el proceso. Además, las opiniones de las asociaciones de pacientes y sociedades científicas ayudaron a reforzar la calidad del contenido de mHeart y la futura escalabilidad a otros hospitales.

En el *tercer estudio* se incluyeron 31 trasplantados cardíacos en fase aguda. La media de edad fue de 54 (SD12) años y la mayoría de ellos era hombres [22 (71%)]. Los pacientes tomaban una media de 13 (SD4) fármacos diferentes por día [rango 7-18]. Un 42% de los pacientes (13/31) no eran conocedores de las consecuencias de no tomar la medicación y 39% (12/31) fueron no-adherentes al tratamiento inmunosupresor. La medida de la validez de contenido mostró excelentes niveles de acuerdo del panel de expertos para los dos cuestionarios (<85%). La adecuación de la versión electrónica respecto a la versión original en papel obtuvo un excelente grado de acuerdo para los cuestionarios Haynes-Sackett ePROMs [Kappa=0.826, *P*-valor<.001] y Morisky-Green-Levine ePROMs [Kappa=1, *P*-valor<.001]. La correlación entre los cuestionarios SMAQ y Morisky-Green-Levine ePROM fue elevada [validez convergente, *Phi*=0.6, *P*-valor<.001], mientras que para el Haynes-Sackett ePROMs fue baja [validez divergente, *Phi*=0.3, *P*-valor=.12]. Mostrando que los dos cuestionarios ePROMs en mHeart miden rasgos diferentes y complementarios de la adherencia al tratamiento farmacológico.

La medida de la fiabilidad de medidas equivalentes mostró una fuerte asociación entre los cuestionarios electrónicos en mHeart ePROMs y los originales en papel [*Phi*>0.7, *P*-valor<.001]. La medida de la reproducibilidad fue moderada [Haynes-Sackett Kappa=0.6, *P*-valor<.002] o débil [Morisky-Green-Levine Kappa=0.3, *P*-valor=.11] debido a una inesperada mejora de las cifras de adherencia a la medicación durante el período del test-retest. En cuanto a la sensibilidad al cambio de los ePROMs, *la estrategia mHeart* mejoró significativamente las cifras de adherencia terapéutica entre un 16% y 26% [*P*-valor<.05]. El análisis del impacto en carga mostró que los ePROMs pueden sobrellevar las principales limitaciones del método tradicional presencial. Por ejemplo, los ePROMs permitieron el registro automático de las respuestas de los pacientes en la historia clínica informatizada del hospital. Esto permitió reducir el tiempo de registro, evitar la interpretación subjetiva del entrevistador y disponer de información en el entorno habitual del paciente y de forma anticipada. La satisfacción global de los pacientes con el programa asistencial y aplicación móvil mHeart fue de 9 (SD2) (score 0-10). Todos los pacientes encuestados [29 (100%)] reportaron que recomendarían mHeart a otras personas trasplantadas.

En el *cuarto estudio* aleatorizado a largo plazo, un total de 180 pacientes trasplantados cardíacos fueron analizados; de ellos, 134 fase crónica [intervención N=71; control N=63] y 46 en fase aguda. La cifra de abandono del estudio fue del 4%. El tiempo medio de seguimiento fue de 1.6 (SD0.6) años. La edad media fue de 55 (SD14) años; el 30% fueron mujeres. De los 117 pacientes que iniciaron el estudio, el 86% seguían usando mHeart cada día al final de este.

En cuanto a la experiencia del paciente con su pauta terapéutica, esta se vio significativamente mejorada, incluyendo: menor grado de incomodidad asociada con la toma de su pauta terapéutica a diario [*P*-valor=.002], el conocimiento de los pacientes del número de tomas de medicación [*P*-valor=.019], nombres de los fármacos [*P*-valor=.006], dosis [*P*-valor=.030] y número de indicaciones recordadas [*P*-valor=.003]. El conocimiento del paciente sobre las consecuencias de olvidos de medicación mejoró en todos los grupos

[*P*-valor<.01] y el número de efectos secundarios reportados por el paciente se vio significativamente reducido a 3 (SD2) al final del estudio y para todos los grupos del estudio [*P*-valor=.000].

En segundo lugar, la cifra de pacientes adherentes al tratamiento inmunosupresor mejoró un 65% en el grupo intervención según el cuestionario SMAQ [OR=2.3 (0.3;19.7), *P*-valor=.000]. Esta mejoría al final del estudio fue significativa comparado con el grupo control (46% versus 85%) [OR=6.7 (2.9;15.8), *P*-valor=.000].

Por último, debido a la posibilidad del seguimiento online a través de mHeart, la necesidad de visitas presenciales con el farmacéutico clínico y la frecuencia del seguimiento presencial se vieron significativamente reducidas en el grupo intervención (65%) respecto al grupo control (35%) [OR=3.4 (1.7;6.9), *P*-valor=.001].

CONCLUSIONES

El valor total de complejidad terapéutica (*total pMRCI-S*) de la población trasplantada cardíaca es el más elevado comparado con cifras publicadas en la literatura para diferentes patologías crónicas. Esta elevada cifra de complejidad se ve influenciada sobretodo por la categoría *tratamiento de las comorbilidades*. El índice pMRCI-S es un método sensible que permite la identificación individual de los factores que determinan la complejidad terapéutica post-trasplante. Esto facilita la selección de pacientes candidatos a estrategias individuales para reducir los valores de pMRCI-S.

Un programa mHealth integral destinado a mejorar el manejo de la medicación post-trasplante y la práctica clínica en poblaciones crónicas multimórbidas con polimedicación fue implementado con éxito en las consultas externas de una unidad de trasplante cardíaco. Las principales barreras fueron entre otras asegurar el adecuado tratamiento y confidencialidad de los datos, reducir tanto la carga de trabajo de los profesionales como la brecha digital de profesionales y pacientes, así como asegurar la interoperabilidad

entre mHeart y la historia clínica del centro. Los pacientes confirmaron que la mayoría de ellos (98%) estaban dispuestos a usar mHeart.

El estudio de la validación de la versión electrónica de los cuestionarios mHeart para medir la adherencia a la medicación mostró que los ePROMs cumplían con los estándares de calidad exigidos. Además, los ePROMs demostraron ser igualmente efectivos en identificar a los pacientes no-adherentes respecto al método convencional presencial. El estudio exploratorio de la viabilidad y eficacia de la intervención clínica en el manejo de la adherencia terapéutica *(la estrategia mHeart)* mostró ser eficaz con un prometedor incremento de adherencia terapéutica del 30%. La eficacia del programa se vio acompañada por un excelente nivel de satisfacción y usabilidad con la estrategia por parte de los pacientes incluidos. Estos resultados soportan el uso de la aplicación móvil y *la estrategia mHeart* en investigación y práctica clínica.

Un alarmante 36% de los pacientes trasplantados cardíacos eran adherentes a la terapia inmunosupresora según el cuestionario SMAQ al inicio del estudio. Además, un 41% de los pacientes refirieron desconocer las consecuencias de olvidos de tomas de su medicación inmunosupresora. Estas cifras confirmaron la necesidad urgente de estrategias innovadoras para hacer frente al problema.

La estrategia mHeart obtuvo un impacto positivo en los resultados de salud preestablecidos. En primer lugar, la adherencia a la medicación mejoró de forma estadísticamente significativa (85%) respecto al grupo control (46%). Confirmando de ese modo que la combinación de diferentes intervenciones multinivel como el uso de técnicas conductuales del cambio dirigidas al paciente empoderado mediante la salud digital, son estrategias sinérgicas que incrementaron la efectividad del tratamiento de mejora de la adherencia a la medicación. En segundo lugar, se obtuvieron mejoras significativas en aspectos relevantes de la experiencia y creencias del paciente con su pauta terapéutica. Finalmente, *la estrategia mHeart* demostró reducir de forma significativa el número de pacientes que precisan ser atendidos de forma presencial en consultas externas. El programa asistencial mHeart se

configura así como una alternativa viable para proporcionar un seguimiento individualizado y anticipado a largo plazo de los pacientes trasplantados cardíacos desde su domicilio.

IMPLICACIONES ACTUALES Y FUTURAS DEL TRABAJO DE TESIS

Como consecuencia de la herencia del trabajo previo de farmacéuticos clínicos desde 1967, la atención farmacéutica centrada en la persona continúa siendo el epicentro de la práctica clínica del servicio de farmacia del Hospital de la Santa Creu i Sant Pau. Actualmente, las autoridades sanitarias han dirigido el punto de mira a la población de pacientes externos de los centros como punto crítico del sistema sanitario en la gestión de la complejidad. Entre las poblaciones de pacientes crónicos, la población trasplantada presenta un elevado riesgo de presentar peores resultados en salud derivados de la multimorbilidad y la complejidad terapéutica. Las guías internacionales demandan a los centros de trasplante contar con farmacéuticos clínicos integrados en los equipos interdisciplinares con el fin de ayudar con el manejo de la complejidad terapéutica a los profesionales sanitarios.

Estos retos han inspirado a llevar a cabo el estudio mHeart y la presente tesis doctoral, con la intención de promover el rol del farmacéutico clínico en los equipos de trasplante y asegurar la presencia del farmacéutico especialista en los centros de trasplante españoles. Y es que la implementación del estudio mHeart permitió visibilizar la figura del farmacéutico a pacientes, familias y a los profesionales que conforman las instituciones sanitarias. Además, la salud móvil resultó ser una oportunidad excepcional para expandir los beneficios de la atención farmacéutica en el sistema sanitario.

No obstante, la aplicación de *la estrategia mHeart* en nuestro centro requirió de un abordaje multidisciplinar. Actualmente, cardiólogos/as, cirujanos/as, enfermeros/as, trabajadores/as sociales, psicólogos/as, nutricionistas, y farmacéuticos/as clínicos trabajan de forma coordinada para mejorar los resultados en salud de la población trasplantada cardíaca del Hospital de la Santa Creu i Sant Pau.

Los proyectos innovadores en las instituciones sanitarias suelen ser prácticas a corto plazo, con una clara tendencia a no ser escalados a la práctica habitual. Esta transición fue, por tanto, una prioridad para el estudio mHeart, una vez demostrado el impacto en resultados en salud. En el caso de mHeart, el modelo fue extendido a la práctica clínica en enero de 2019. No obstante, la transición del proyecto de investigación a la práctica clínica habitual fue exigente. Comportó ajustes dirigidos por el servicio de farmacia y la unidad de trasplante cardíaco respecto a la financiación y cambios estructurales en cuanto al equipo, los procesos y los departamentos de la institución. Con la necesidad, además, de contar con la opinión de los pacientes, otros profesionales y los representantes de las instituciones.

El modelo mHeart descrito en esta tesis ha sido escalado al seguimiento de otras poblaciones de alta complejidad en el Hospital de la Santa Creu i Sant Pau. Los nuevos proyectos de salud digital aplicados al paciente complejo ambulatorio tienen como objetivos comunes la mejora de las rutas asistenciales, la mejora de la seguridad y efectividad de la terapia o la promoción del empoderamiento de los pacientes y la comunicación entre profesionales-pacientes/familias. La plataforma mHeart ha sido además aplicada por diferentes instituciones sanitarias como base tecnológica para desarrollar sus propias versiones dirigidas a diversas poblaciones de pacientes en España.

Por todo ello, las implicaciones del estudio mHeart y del modelo asistencial de salud digital establecido en la presente tesis son un prometedor punto de partida para el establecimiento de una innovadora vía para proveer asistencia de calidad a poblaciones de elevada complejidad en nuestro entorno, con el soporte de la salud digital y promovido por el propio sistema sanitario.

INTRODUCTION

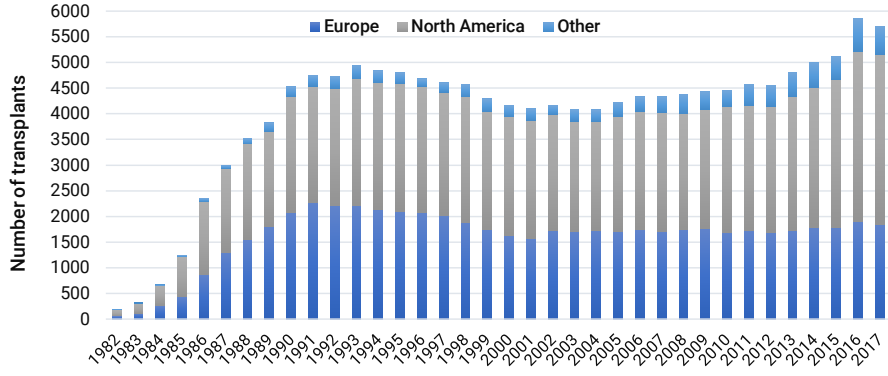
1. INTRODUCTION

1.1. HEART TRANSPLANT

1.1.1. HEART TRANSPLANT RATES

Solid organ transplantation could be the best, and frequently, the only life-saving treatment for end-stage heart failure. (2) Heart transplantation (HTx) was considered a 'fantastic dream' in the early 1950s. (3) Nowadays, it is the treatment of choice for selected patients with advanced heart failure. According to international records, the majority of centers are performing 10-19 HTx per year. (4) This volume has been increasing steadily worldwide for more than a decade (Figure 1) (4) reaching 7,000 procedures during 2017, a third of them performed in Europe. (5) The first HTx in Spain was realized in 1984 at the Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. Since then, more than 8,173 procedures have been performed, 32% of them in the last decade. Around 300 adult and pediatric procedures are performed annually in Spain, 50% of them in emergency situations. (5)

Figure 1: Number of adult and pediatric heart transplants by year and location.



Data from the International Society Heart and Lung Transplant (ISHLT) annual report 2019 (adapted). (4)

1.1.2. THE SOLID ORGAN TRANSPLANT "SPANISH MODEL"

Since the National Transplants Organization (ONT) was created in 1989, Spain has progressively reached the highest rate of organ donation especially in the last decade. Figures published for 2017 reveal that 2,183 people became organ donors last year following their death. That is a rate of donation in Spain of 46.9 pmp (i.e. million people in the population), and it demonstrates that Spain has the highest rate worldwide and is maintaining its first position in transplant organ donation over the years. Currently, this is a challenge given the context of the decline in the incidence of brain death and the changes in end-of-life care practices in Spain since the beginning of the century. (2,6)

The Spanish model is an international reference point. The key elements of this model have been widely published to facilitate scalability to other countries. Its success appears to derive from a specific organizational approach to ensure the systematic identification of opportunities for organ donation, and its transition to actual donation. But also due to a successful promotional campaign increasing public support for the donation of organs after death. (2,6) Some of the most relevant elements of this model to note are showed in Textbox 1. (7)

Textbox 1: Some of the most relevant elements of the Spanish model. (7)

- The coordination network (national, regional and hospital level).
- The specific coordinator profiles.
- The support of a central agency.
- Frequent audits.
- Training of professionals.
- Strategy on mass media.
- The hospital reimbursement for donation activities.

According to the ONT annual report (2017) the organization around the process of deceased donation is the key to the future success of the Spanish system. For instance, constant improvements are needed to maintain these rates such as the last relevant factors presented in Textbox 2. (2)

Textbox 2: Improvements to maintain the rate of donation in Spain according to the ONT annual report (2017). (2)

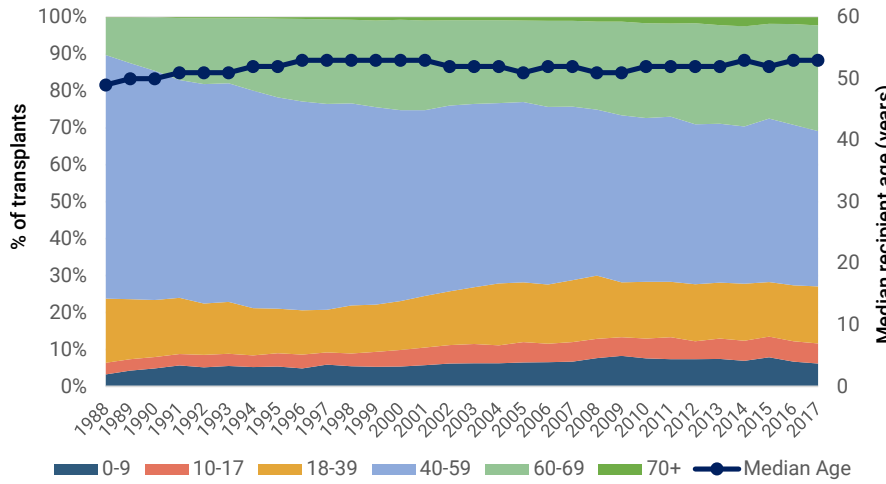
- Promoting the early identification of possible organ donors from outside the Intensive Care Unit.
- Considering elective non-therapeutic intensive care and to incorporate the option of organ donation into end-of-life care.
- Facilitating the use of organs from expanded criteria and nonstandard risk donors.
- Developing the framework for the practice of donation after circulatory death.

1.1.3. SURVIVAL IN THE HEART TRANSPLANT POPULATION

Several factors, such as advances in surgical techniques, improvements in immunosuppressive treatment and more stringent infection controls, have permitted an increase in survival rates since the first procedures were performed. Median survival for adult HTx performed in 2002-2009 exceeds 12 years, and survival conditional to 1 year remains above 50% at 14 years of follow-up. (4) In Spain, a statistically significant improvement in the first year and late survival is observed prior to 2008 [*P*-value<.001]. Among 2008-2016, a trend was detected in improving general survival in comparison with previous triennium [*P*-value=.056]. This tendency towards improvement seems to be related to a decrease in acute deaths depending on the control of infection and acute rejections. In addition to a decrease in primary graft failure due to a reduction in ischemia time and aided by the use of mechanical circulatory assistance. (5)

The mean determinants on survival during 2008-2017 in Spain were the age of the HTx recipients and the type of mechanical circulatory support available before the transplant. Indeed, patients 60 years old or older at the time of the HTx are at increased risk of mortality [70%, *P*-Value=.001]. (5) According to the ISHLT 2019 report, similar trends are been observed internationally. (4) These figures cause concern, as the age of the recipients has significantly increased in Spain, around a mean of 52 (range 16-73) years old in 2017, (5) and compared with similar figures internationally (Figure 2). (4)

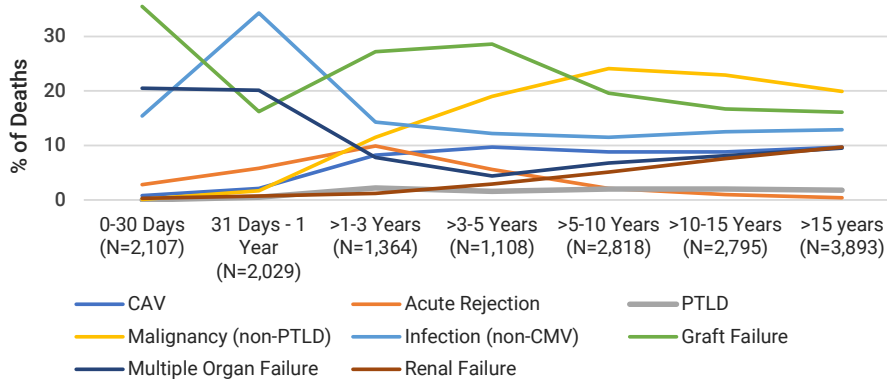
Figure 2: Adult and pediatric heart transplants recipient age by year of transplant.



Data from the International Society heart and Lung Transplant (ISHLT) annual report 2019 (adapted). (4)

The causes of death vary with time post-HTx following similar tendencies in Spain and worldwide (Figure 3). Graft failure is the highest cause of death during the first 30 days (44%), followed by infectious complications in the first year (23%). Between the first and fifth year, cardiac allograft vasculopathy (CAV) (28%) and malignancy (21%) are the main causes of death and increases over time from the initial transplant. (4,5) Acute rejection rates causes 8% of all the HTx deaths in the first year, and this statistic is 3 times higher between the first and fifth year (18%). (5)

Figure 3: Relative incidence of leading causes of death in adult heart transplant (January 2010 – June 2018).



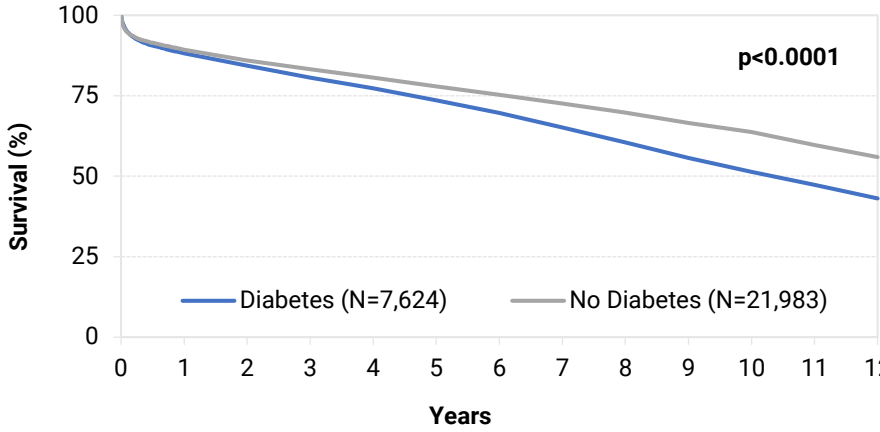
Data from the International Society heart and Lung Transplant (ISHLT) annual report 2019 (adapted). (4)

1.1.4. MORBIDITY IN THE HEART TRANSPLANT POPULATION

The success of a transplant procedure involves not only survival, but the quality of mental and physical functions are also important determinants of the recipient's quality of life (QoL). In recent decades, the improvement on HTx recipient's life expectancy has increased the clinical team's attention in long-term care. Due to a greater complexity of this patient group, the functional status and QoL of HTx recipients remain lower than in the general population. (8) Thus, new strategies are needed to achieve long-term morbidity-free survival and an acceptable QoL after transplantation. (9,10)

According to the last international HTx report, morbidity after transplant is related with some relevant factors. First, post-transplant length of hospitalization is increasing, especially in Europe, with a higher proportion of patients with lengths of stay >21 days. This may be related to the increasing procedures involving higher risk donors and recipients observed between 2013-2017. Second, the development of CAV but also diabetes and severe renal dysfunction (defined as serum creatinine>2.5 mg/dl, chronic dialysis, or renal transplant) are important post-transplant morbidities directly related with poor survival rates (Figure 4). (4)

Figure 4: Kaplan-Meier survival by recipient diabetes mellitus in adult heart transplants (January 2005 – June 2017).



Data from the International Society heart and Lung Transplant (ISHLT) annual report 2019 (adapted). (4)

Five years after HTx, 95% of the patients develop hypertension, 81% hyperlipidemia, 33% chronic kidney failure and 32% diabetes. Furthermore, almost half of recipients have CAV by 10 years post-transplant. (11) Indeed, although CAV has an immunologic origin, it has been also related to comorbidities such as long-standing high blood pressure, or alteration of serum lipid profile. It should be noticed that according to the International Society of Heart and Lung Transplantation's (ISHLT) international registry, CAV was significantly lower in the last 12 years suggesting better preventive therapies. (4) Therefore, it is more than justified to direct efforts on strategies to improve long-term management of cardiovascular risk in these patients. (12,13)

The international guidelines of the ISHLT deals with the more frequent comorbidities after HTx, typically caused by immunosuppressive treatment. (14) Nevertheless, similar to other chronic populations, the increase on patients' mean age observed in recent years is related with emerging new-onset comorbidities. Moreover, management of chronic comorbidities led to an inevitable requirement for sharing post-transplant patient's management with other professionals and levels of care. (15)

1.1.5. ADHERENCE TO BEHAVIOR SELF-CARE IN THE HEART TRANSPLANT POPULATION

Living after HTx is also challenging since it encompasses several behaviors that patient must incorporate into their routine for their lifetime (Table 1). Thus, patients who regularly attend appointments (i.e. in-clinic visits, tests and blood testing) are at a lower rate of acute rejection (2%) compared with 57% in recipients with less adherence. (16) Furthermore, several non-pharmacological regimens are highly recommended including abstaining from alcohol, smoking cessation, increasing moderate physical activity and introducing healthy eating habits. Likewise, recipients are asked to monitor for signs and symptoms related with potential complications or to avoid new onset comorbidities.

Table 1: Major medical complication and recipients' responsibilities after HTx. (14,16)

Complication after HTx	Patients' behaviors to be adherent
Graft rejection	- Clinic appointments for regular exams and tests (e.g. Endomyocardial biopsy and blood tests). - Take medications as agreed with professionals. - Monitor body temperature.
Opportunistic infection	- Monitor body temperature. - Take medications as agreed with professionals. - Follow hygiene and dietetic recommendations.
Malignancy	- Follow sun protection recommendations. - Healthy lifestyle avoiding smoking and moderate drinking.
Toxicity of immunosuppressive drugs	- Clinic appointments for regular blood test and assessments. - Take medications as agreed with professionals. - Monitor blood pressure, glycaemia and weight. - Follow life-style recommendations such as exercise and diet.
Cardiac allograft vasculopathy (CAV)	- Follow life-style recommendations such as exercise, diet and smoking to prevent hypertension, diabetes, hyperlipidemia and obesity. - Take medications as agreed with professionals. - Clinic appointments for regular blood test and assessments. - Follow the recommendation for cytomegalovirus prevention.

Therefore, it would be a great achievement if patients succeed in taking care of all these aspects of their lives. Indeed, a meta-analysis showed that 28% of HTx recipients are nonadherent to physical activity and 34% do not follow a correct diet. (17) The prevalence of cigarette smoking ranges from 6% to 35%, and the usage of alcohol or illegal drugs ranges from 7% to 25%. (16) Moreover, nonadherence to blood tests has been seen in 22% to 59% of recipients, while 3% to 27% do not attend appointments. (16) In 2012, as many as 36 recipients with follow-up in our HTx center were included in the BRIGHT international study. A center intermediate report of the BRIGHT study (non-published) showed that 5% of our patients consumed alcohol, 6% were smokers and 78% did not protect themselves from the sun. Moreover, as many as 33% of patients were identified as nonadherent to diet and 56% did not perform any physical activity. Even though the sample was small, this report was a starting point to figure out how important is to measure risk factors in clinical practice. (18)

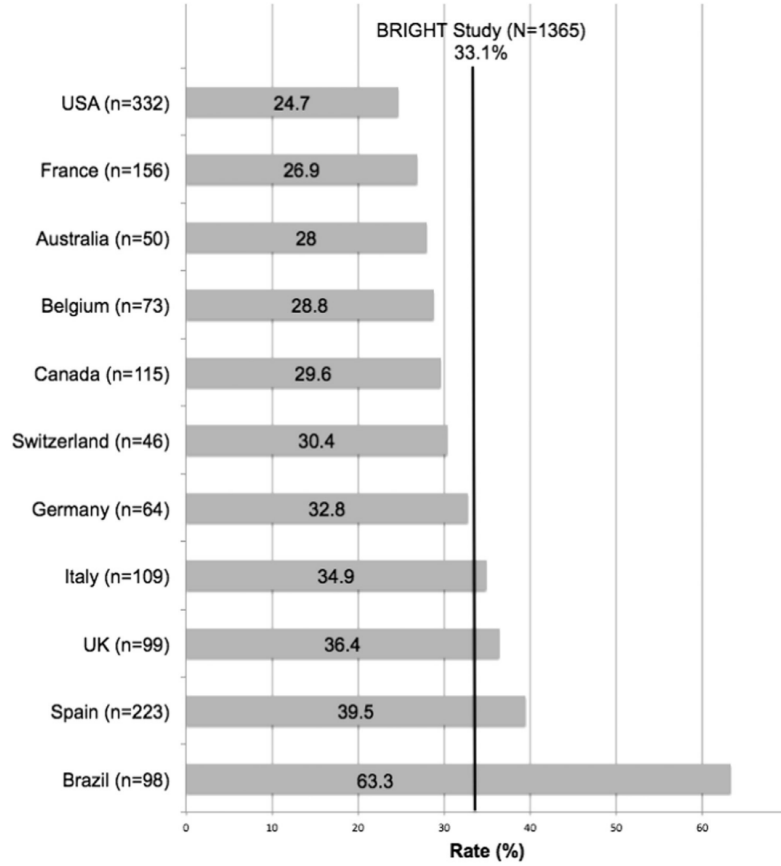
Some of these behaviors have already demonstrated a significant impact on survival, such as diabetes (Figure 4), cigarette smokers' history, and body mass index. Moreover, according to the ISHLT international registry other relevant determinants such as blood pressure may still remain to be proven because there is a lack of data currently available. (4) Another important recognized factor which improves health outcomes post-transplant is the fact that the patient may be able to seek medical attention when a major complication occurs. (16) Therefore, the patient's self-efficacy to recognize major complications and manage them are critical behaviors post-transplant. Which are, indeed, highly influenced by the patient's skills reached and, most importantly, the team efforts to provide to the patients an adequate level of health literacy prior and post-HTx.

1.1.6. HEALTH LITERACY IN THE HEART TRANSPLANT POPULATION

The BRIGHT study showed that Spain was the second country with the lowest health literacy compared with other centers from 11 countries and 4 continents (Figure 5). Worryingly, as many as 40% of recipients in Spain have inadequate health literacy, which is, indeed, related to determinants of poorer health outcomes as they encounter difficulties in following regimens and in communicating effectively with health providers. (19)

Since the Spanish donation system has been the flagship internationally, this is a low-quality marker that should be drastically changed. Strategies to reduce this rate are focused on reinforcing the clinician's communication and the patient's skills. In this sense, there are effective strategies such as using everyday non-technical language, limiting the information to 3-5 important key points, and using the teach-back method to identify information lapses or misunderstandings during the visits. (20) Moreover, offering the patient additional educational material is also a popular widely used tactic. (21) Nevertheless, current and more innovative tools such as games, on-line self-educational websites or apps will have an increased potential.

Figure 5: Variability in the prevalence of inadequate health literacy[a] across the 11 countries in the BRIGHT Study.



[a] Health literacy (HL) measured using the 1-item Subjective Health Literacy Screener; wherein inadequate HL was operationalized as being confident in filling out medical forms ranging from *None to Some of the time*. Inadequate Health Literacy was operationalized as being confident in filling out medical forms *none/a little/some of the time* (HL score of 0-2). Image courtesy of Cajita et al., 2016. (19)

1.2. THERAPEUTIC COMPLEXITY IN THE HEART TRANSPLANT POPULATION

1.2.1. THE STANDARD PHARMACOLOGICAL REGIMEN IN THE HEART TRANSPLANT POPULATION

In the HTx population, recipients are in need of lifelong immunosuppressive therapy in order to avoid rejection episodes, and several other treatments to prevent or treat comorbidities. Medication regimen after HTx could be classified in 3 categories as detailed in Figure 6: 1- *Immunosuppressive medication*; 2- *Other treatments established in the post-HTx protocol*; and 3- *Drugs to treat comorbidities*, including over-the-counter products. (22) Increasingly, patients are also taking complementary health therapies (CHA), such as natural plants or homeopathic treatments. (23)

The combination of various maintenance immunosuppression therapies including corticosteroids, calcineurin inhibitors, anti-metabolites and mTor-inhibitors is the most common course of treatment. (14) This approach is beneficial because action mechanisms are synergistic and it enables a reduction in the doses of each individual drug, mitigating potential toxicity and dose-related side effects.

Nowadays, according to the ISHLT recommendations, the standard immunosuppressive regimen is based on calcineurin inhibitor-based therapy (i.e. tacrolimus or cyclosporine) and an antiproliferative immunosuppressant (i.e. mycophenolate sodium (MPS), mycophenolate mofetil (MMF) or azathioprine). However, the use of tacrolimus is increasing nowadays with 75% of recipients taking tacrolimus-MMF/MPS combination during the first year post-HTx. Although no significant difference in long-term survival was observed in patients treated with tacrolimus versus cyclosporine-based regimens at one year, rejection rates at 1 year post-HTx were lowest in recipients treated with tacrolimus-MMF/MPS than cyclosporine-MMF/MPS. (4) Other immunosuppressive regimens could be based on mammalian target of rapamycin inhibitors (everolimus or sirolimus), which are used to reduce the onset and progression of cardiac allograft vasculopathy. (14)

Figure 6: The standard pharmacological regimen in the heart transplant population based on the center protocol and the International Society of Heart and Lung Transplantation (ISHLT). (14)

Therapeutic group 1 Immunosuppressant drugs	**Therapeutic group 2** Treatment associated with HTx	**Therapeutic group 3** Other treatments for comorbidities
☐ Cyclosporine or tacrolimus	☐ Calcium/vitamin D	☐ Antidepressants
☐ Everolimus or sirolimus	☐ Statins	☐ Hypnotics and other drugs for sleep disorder
☐ Prednisone	☐ Aspirin (acetylsalicylic acid)	☐ Antihypertensive drugs
☐ Mycophenolate sodium (MPS) or Mycophenolate mofetil (MMF)	☐ Valgancyclovir (prophylaxis)	☐ Antiarrhythmic drugs
☐ Azathioprine	☐ Cotrimoxazol + folinic acid (prophylaxis)	☐ Antidiabetic drugs
	☐ Nistatine (bucal) (prophylaxis)	☐ Anticoagulants
		☐ Diuretics
		☐ Laxatives and antidiarrheal drugs
		☐ Antiacids
		☐ Pain drugs
		☐ Magnesium or other minerals and vitamins
		☐ Osteoporosis drugs
		☐ Others

Corticosteroid therapy is the third drug to consider on the triple regimen after-HTx. High doses of intravenous metilprednisolone, and subsequently oral prednisone, are widely used to prevent early acute rejection. Nevertheless, taking a long-term approach, early weaning, very low dose maintenance therapy or even corticoids avoidance are acceptable therapeutic approaches based on the ISHLT recommendations. (14) For instance, corticosteroid weaning is attempted if there are significant adverse effects and no recent rejection episodes. (24) According to the ISHLT international registry, approximately 80% of patients are reported to be taking a steroid at one-year post-HTx. Although a long term corticosteroid therapy appears to be decreasing, (4) low-dose maintenance corticosteroid therapy is still used in Spain in 64% of the cases (1984-2016). (5)

In addition, as many as 50% of HTx recipients received immunosuppressive induction therapy at the time of transplantation during the last decade, according to the ISHLT international registry. (4) In Spain, solely 17% of the recipients were induction free in 2017. The most frequent induction therapy is basiliximab, used in 76% of HTx recipients the same year. (5)

Furthermore, HTx recipients without intolerance or allergies receive lifetime treatment with; (i) calcium combined with vitamin D as prophylaxis for corticosteroid-induced bone disease and to prevent osteoporosis. The ISHLT also recommends bisphosphonate in patients taking >5mg/d prednisone for 3 months; (14) (ii) a statin to reduce CAV and to improve long-term outcomes regardless of lipid levels. Indeed, the statin initial doses are lower than those recommended for hyperlipidemia treatment; (14,25) and (iii) an antiplatelet therapy with aspirin 100 mg daily to prevent CAV. (11,26)

The acute phase after HTx is characterized by higher doses of immunosuppressive regimens, leading to an increased risk of opportunistic infections. Thus, according to the center protocol and based on ISHLT recommendations, prophylaxis is standardized for all HTx recipients during the most at risk period post-transplant. Infection prophylaxis includes nystatin oral solution for mucocutaneus candidiasis, valganciclovir to prevent from *Cytomegalovirus* and trimethoprim plus sulfamethoxazole, which is active ahead of *Pneumocystis jiroveci*, *Toxoplasma gondii* and *Nocardia*. This infection prophylaxis may be reinstituted when there is an increased risk of infection due to rescue immunosuppression treatment. In other centers, different infection prophylaxis regimens may be considered. Moreover, depending on the serological status, recipients may need more complex prophylaxis regimens and higher effective drugs. (11,14)

Moreover, apart from such therapies, several other treatments may be considered depending on the comorbidities such as diabetes, hypertension, gout, depression or osteoporosis treatment. (11,14)

1.2.2. THERAPEUTIC COMPLEXITY RATES IN THE HEART TRANSPLANT POPULATION

The final therapeutic goal of immunosuppression is to maintain the balance between over-immunosuppression (i.e. organ toxicity, adverse drug events, infections and malignancies) and under-immunosuppression (i.e. increased risk of rejection and graft loss). Thus, a close re-evaluation of the immunosuppressive treatment is needed for lifetime post-HTx. In this way, the pharmacokinetic monitoring of anticalcineurin drugs allows, in usual practice, the possibility to individualize doses considering the time elapsed since HTx, malignancies or active infections among several other relevant individual factors.

In the early stage post-HTx, patients should be closely monitored because an appropriate level of immunosuppression should be attained. In this phase, potential drug-drug or drug-disease interactions are possible. Indeed, drug-drug interactions are common since immunosuppressive treatments are metabolized by P450 enzymes entailing a risk of toxicity or loss of effect. Thus, the recognition and management of these interactions requires the full attention of health providers. (27) Moreover, since post-transplant entails a very complex medication schedule and awareness, discharge time could be challenging for both patients and caregivers. Thus, clinical teams should provide the skills needed during hospitalization, at discharge and during the earliest months post-HTx to promote patient self-efficacy.

Over the long-term, drug-drug interactions and adverse drug-effects are also common in this population. (27) Therapeutic follow-up provided by the transplant caregivers is critical since regimen modifications are needed because new drugs to treat comorbidities, but also because dosage individualization of the immunosuppressant therapy. In addition, compliance with treatments should be ensured since is a huge determinant of therapeutic success post-HTx. In summary, the great therapeutic complexity after HTx leads to a need for the clinical team lifetime monitoring of patients' regimens adequacy.

A standard regimen after HTx involves an average of 10 drugs and a third of patients taking over 16 drugs five years post-HTx. (28,29) Many methods for assessing the therapeutic complexity of chronic patients have been used. However, experience in the usage of tools for measuring therapeutic complexity after solid organ transplant remains limited. The number of prescribed drugs is a commonly used method in literature and usual practice. It is considered *polypharmacy* when the patient takes more than 5 drugs and *high therapeutic complexity* when the patient takes more than 8 different drugs per day. (30) Nevertheless, these cut-offs are not useful in HTx populations, with a majority of recipients exceeding these rates. The term *therapeutic risk* has been also defined as the likelihood of patients at risk of Negative Outcomes associated with Medication (NOM) because treatment. (31,32) However, this is a subjective definition which varies among literature including different criteria and ranges regarding age, drugs count, multimorbidity, patients residing in a care home (i.e. being frail and with polypharmacy) (33) or terminally ill among others. (34,35)

In 2004, the patient Medication Regimen Complexity Index (pMRCI) was validated and became the gold standard in chronic populations. (36,37) Mainly because this quantitative index allows to differentiate between levels of therapeutic complexity in therapeutic regimens with the same total number of drugs. (29) Moreover, it takes into account pharmaceutical form, dosing frequency and additional instructions that the patient is given, thereby providing useful information about the complexity of determinants in individual patients. The value of the pMRCI increases in accordance with the complexity of the therapeutic regimen with no maximum value or cut-off values as predictors of high or low therapeutic complexity.

In adult transplantation, only 2 studies used the pMRCI index which reported values from 29-37. (29,38). In the case of patients with high blood pressure, HIV infection, diabetes mellitus or geriatric patients suffering from depression, lower pMRCI rates of 18, 22, 23 and 25 respectively have been reported. (39) These differences pointed that after a solid organ transplant, the levels of therapeutic complexity may be higher than other chronic populations taking the same number of prescribed drugs.

1.2.3. THERAPEUTIC COMPLEXITY IMPACT ON HEALTH OUTCOMES

Different studies have shown that high therapeutic complexity, measured as pMRCI, has a large impact on adherence rates, (40–42) adverse drug events, (43–46) hospitalization (44–46) and mortality (47) in different chronic patient populations.

The predicting factor values of low and high therapeutic complexity vary considerably in accordance with patient populations. In the case of adult outpatients, Ferreira et al. (48) propose a pMRCI value of 24 as a predictor factor for maximum therapeutic complexity and a need for prioritization. Nevertheless, in elderly patients higher cut-off values of 33-35 have been defined for predicting hospital readmission together with other negative consequences of therapeutic complexity. (48) If this cut-off value was applied to the therapeutic complexity rates observed in the transplant population, almost all the recipients would need to be prioritized to intervene and reduce complexity. Therefore, for future studies, it would be worthwhile defining the predicting values for greater risk of readmission or mortality in the transplant population, as is already the case for other populations.

Dosing frequency impacting on low adherence has been studied in the transplant population. (49–51) The immunosuppressive drug tacrolimus is presented in a regular (each 12 hours regimens) but also extended release formulation (each 24 hours regimens). Thus, the pharmacy industry and independent researchers studied the impact on health outcomes of interventions to simplify dosing frequencies. This strategy has been shown to improve adherence in HTx and the quality of life post-Tx by 14%. Nevertheless, there are also other studies which did not find such differences switching presentations. (52–56) It is likely that therapeutic complexity post-transplant is far more complex than the frequency of immunosuppressive treatment. However, since there is evidence that points that one to two times per day medication schedule may be associated with adherence improvement, an effort to reduce the overall schedule intakes should be performed.

(57) Furthermore, among other interventions, optimization of drug prescribing, not only implies frequency reduction, but also deprescribing efforts, tailoring additional instructions or to be aware and avoid the prescribing cascade.

Regimens simplification in chronic conditions is paramount since Menditto et al. (58) observed that drugs may be the cause of multimorbidity. Their study demonstrated that taking specific drugs in young and adult populations, are related with 6 patterns of diseases; respiratory, cardiometabolic, endocrinological, osteometabolic, and mechanical pain. Moreover, the authors highlighted that drug-drug interactions and prescribing cascades may be potential underlying factors of such associations. These results may be highly useful in transplant clinical practice to better identify inappropriate polypharmacy.

Is well known that immunosuppressive drugs are commonly related with electrolyte disturbances, gastrointestinal disorders and new onset nephrotoxicity, diabetes, hypertension, hyperlipidemia or osteoporosis among other relevant comorbidities. Based on the results obtained by Menditto et al. (58) drugs to treat comorbidities clearly should also have a negative effect on morbidity-free survival in chronic HTx. Nevertheless, the effect of chronic treatments that recipients take every day to treat comorbidities, on multimorbidity levels post-transplant has not been studied.

In summary, the pMRCI score has great potential in transplantation because it permits the identification of candidates for medication therapy management interventions. (59) But also, because the index subscores may identify the risk factors guiding to a targeted optimization of treatment regimens. Fortunately, the pMRCI index has been validated for the Spanish population (22) enabling its applicability in the management of therapeutic complexity in our transplant population.

1.3. ADHERENCE TO MEDICATIONS IN THE HEART TRANSPLANT POPULATION

1.3.1. RATES AND IMPACT OF MEDICATION NONADHERENCE IN THE HEART TRANSPLANT POPULATION

Sub-optimal medication adherence is often a main obstacle in successful pharmacotherapy, and particularly when the problem is unrecognized by health professionals. (60) Medication nonadherence (MNA) rates after a solid organ transplant increases over time, (56) thus a proactive lifelong monitoring and management of nonadherent recipients is needed by the transplant center lifelong. Immunosuppressant MNA entails serious risks post-HTx since it has a detrimental impact on poor quality of life (61) and is a direct cause of late acute rejection, graft loss and death. (17,28,56,62). Any time post-HTx, MNA demonstrated to be an independent risk factor for acute rejection episodes and CAV during 3-5-years follow-up period. MNA showed to be the key determinant in 90% of late acute rejection episodes (>1 year) and in 13% to 36% of all deaths. (16)

MNA to immunosuppressive therapy rates are alarming after HTx, ranging between 15% to 50% in nonadherent recipients. (62) These figures vary significantly depending on the assessment method and the definition of the term *medication adherence* used in literature. (17) For instance, De Bleser et al. in HTx population used several assessment methods obtaining highly different MNA rates. Based on these results, as many as 37% recipients were classified as nonadherent by self-reporting using the BAASIS questionnaire, 43% recipients by nurses' estimation, 22% by assay methods, 67% by a composite measure of nonadherence and 35% measuring MNA by electronic assessment. (63)

In view of the detrimental impact on health outcomes after HTx, these rates are no longer acceptable. Furthermore, on the contrary, as other prevalent chronic diseases, partial adherence in the transplant population (<100% of the intakes scheduled) is not enough to ensure the graft survival. (64) This is because, minor variations on immunosuppressant treatment (<98% of the

intakes scheduled) have been associated with detrimental health outcomes in the heart (65) and the renal transplant populations. (66) Therefore, daily optimal adherence to immunosuppressive treatment is a real challenge for our patients. (18)

The impact on graft loss of MNA is typically underestimated, primarily because the correlation between them is difficult to assess since several mechanisms are involved (Figure 7). This was demonstrated in a study in renal transplant population were clinicians reported MNA as the cause of graft loss in solely 2% of the cases according to clinical practice, compared with a higher rate of 35% of cases according to a second retrospective review of the same sample. (64) It is important to observe that while for renal recipients there are possible treatments after a graft failure episode (i.e. dialysis or re-transplant), in HTx recipients a graft failure episode becomes life-threatening. Furthermore, MNA may also impact on other relevant health outcomes post-HTx. However, as there is not an immediate cause-effect association, it is difficult to attribute and to quantify a correlation effect.

Figure 7: **Mechanisms by which nonadherence affects graft outcome.**

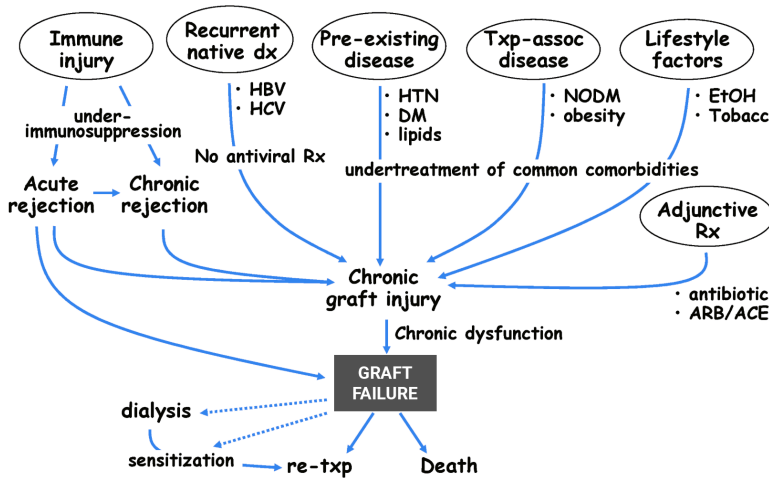


Image courtesy of Fine et al., 2009. (64)

Abbreviations: HBV, hepatitis B virus; HCV, hepatitis C virus; NODM, new onset diabetes mellitus; ARB/ACEI, angiotensin receptor blockers/angiotensin-converting enzyme inhibitors.

Given the high rates of MNA and the serious consequences post-HTx observed, medication adherence is a unique problem which warrants further investigation. This may include well-designed studies to assess the relationship between immunosuppressive treatment MNA and clinical outcomes post-HTx. (64) These results will indicate to practitioners the actual rates in the catchment area and the urgent need for improvements in current healthcare pathways.

The economical cost of MNA is also a reason for all health authorities to address efforts to reduce MNA rates in the transplant population. Data on economic impact on MNA in the HTx population is scarce. (56) However, in the renal field, it was estimated that the cost associated with a kidney failure is $50,938, while maintaining the organ function costs $8,550. (56) Even more, the cost of the total number of graft failures caused by MNA in first year post-renal transplant recipients, amounts to $100 million annually. Unfortunately, financial implications of MNA in HTx populations are not available and are urgently needed in this direction.

1.3.2. ADHERENCE TO MEDICATION DEFINITION AND IMPLICATIONS IN THE SOLID ORGAN TRANSPLANT POPULATION

Progress in the medication adherence field has been hindered by variability in methodology and also poor and incomplete reporting of medication adherence research. (60,67) These many different views of MNA in literature made comparability difficult between studies and also to reach universal conclusions. (68) Regarding terms to define the patient-relationship with medication have been used i.e. *adherence*, *consistency*, *concordance*, etc. Likewise, many definitions have been applied in literature since Hippocrates (Ca 460 BC-370 BC) noticed that “a discrepancy between patients’ behavior and medicines prescribed should maintain clinicians aware”. (Figure 8) (60)

Figure 8: Timeline of changes in terminology for deviations from prescribed dosing regimens' medication.

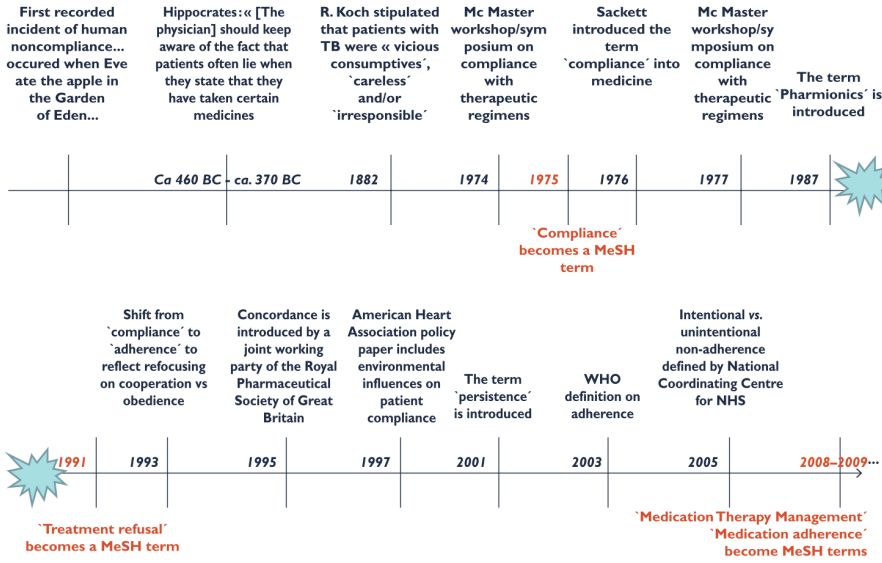


Image courtesy of Vrijens et al., 2012. (60)

The World Health Organization's (WHO) *adherence* definition (2003) is "the extent to which a person's behavior (i.e. taking medication, following a diet, and executing lifestyle changes), corresponds with agreed recommendations from a health care provider". (69) This definition is relevant because it includes all the health-related behaviors beyond taking drugs. But also, it implies the patient agreement on the decisions and the understanding of the information given by the professionals. Based on this definition, health providers should consider there is much more non-patient related risk factors determining MNA. Therefore, the WHO definition suggests that for greater success with medication adherence management, MNA responsibility should be shared with patients.

According to the other terms used in literature, the WHO defined *compliance* as "the extent to which the patient's matches the prescriber's recommen-

dation". *Compliance* is widely considered a paternalistic term not reflecting the actual patient's role in health management. *Concordance* instead is defined as "an agreement reached after negotiation between a patient and a healthcare professional that respects the beliefs and wishes of a patient in determining whether, when and how medicines need to be taken". (69)

Throughout this thesis work, we will use *adherence* to medications or lifestyle rather than other terms. However, it should be noted that the term *concordance* may be used as a synonym reflecting patient's agreement with professionals and active participation on adherence decisions.

In the transplant field, the nonadherence Consensus Conference Summary Report (2009) focused on immunosuppressive therapy adherence. (64) Based on this report, the MNA definition was the "deviation from the prescribed medication regimen sufficient to influence adversary the regimen's intended effect". This is an interesting definition because it is focused on the efficacy of the therapeutic treatment pointing out the real impact of MNA in health outcomes of the transplant population. Moreover, this definition did not mention the patient, as he/she is not the only one responsible for MNA.

More recently in 2012, the ABC taxonomy was published for describing and defining *medication adherence* in the general population. (60) Based on this taxonomy, the European Society for Patient Adherence Compliance and Persistence (ESPACOMP) developed the ESPACOMP Medication Adherence Reporting Guidelines (EMERGE) reporting criteria. (70) The EMERGE guidelines, focused on increasing the transparency and consistency of adherence reporting in research, defined *medication adherence* as "the process by which patients take their medications as prescribed" and divided the term into initiation, implementation and persistence. (Table 2)

Table 2: Medication adherence phases and definitions according to the European Society for Patient Adherence Compliance and Persistence (ESPACOMP) Medication Adherence Reporting Guidelines (EMERGE). (60)

Initiation	Whether the first dose is taken (binary variable "adherent/ nonadherent").
Implementation	The extent to which a patient's actual dosing corresponds to the prescribed dosing regimen: i.e. omitting single or consecutive doses, delays in medication intakes, or self-initiated dose changes as reduction or increase of dosing.
Persistence	The early discontinuation of the treatment without the clinician intervention.

Moreover, the broadly used term *management of adherence* was also standardized as "the process of monitoring and supporting patient's adherence to medications by health care systems, health providers, patients, and their social networks". More details about the process of management of adherence are provided in Figure 9. Finally, a less used term is *adherence-related* sciences which refers to MNA assessment: "the disciplines that seek understanding of the causes or consequences of differences between prescribed (i.e. intended) and actual exposures to medicines". (70)

Figure 9: Illustration of the process of medication adherence (light blue) and the process of management of adherence (dark blue).

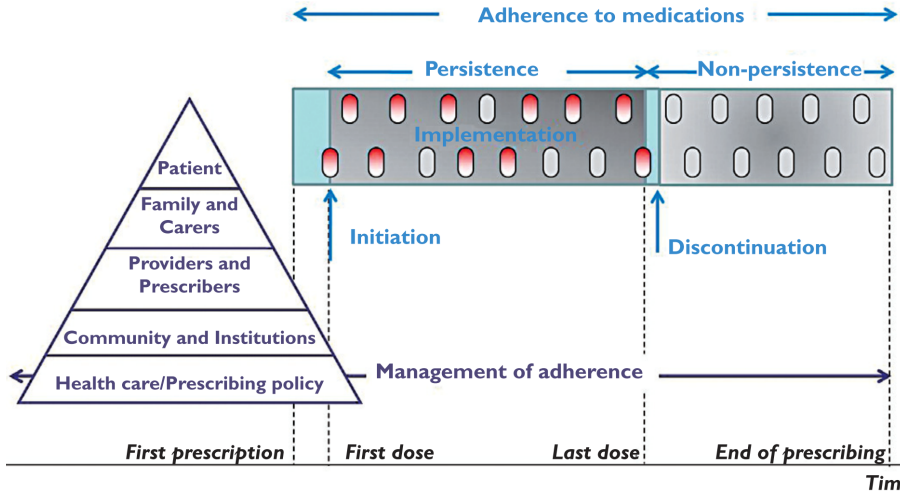


Image courtesy of B. Vrijens et al., 2012. (60)

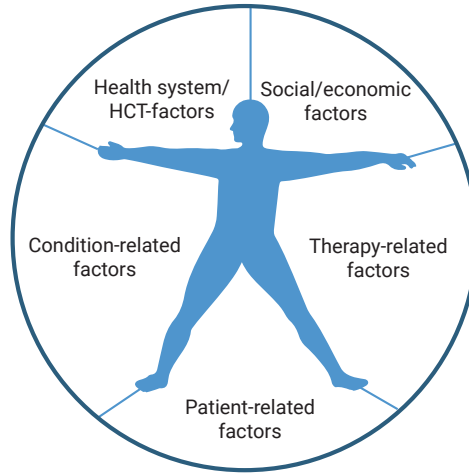
In contrast with other chronic conditions, it should be noted that MNA to immunosuppressive therapy in the transplant population also implies poor regularity of intakes. Minimal delays in the prescribed timeframes and in not taking the drug have been linked with decreased graft survival. (71,72) Any deviation over ±2 hours of the 24 or 12 hours immunosuppressive regimen is considered to be a high variability in HTx. (73) Recent data in renal transplantation suggest that ±4 hours may be more relevant, (74) however it is recommended to continue with the ±2 hours interval since MNA is often underreported. (71)

1.3.3. DETERMINANTS OF IMMUNOSUPPRESSANTS MEDICATION ADHERENCE IN THE SOLID ORGAN TRANSPLANT POPULATION

Determinants for medication adherence in chronic populations can be classified into 5 dimensions; i.e. patient, socioeconomic, disease, treatment and healthcare setting/provider. (69) (Figure 10) A qualitative research focused

on identifying the modifiers of therapeutic conduct on patients with chronic comorbidities was performed in the same catchment area of Barcelona (directed by the Pharmacy Department of the Hospital de la Santa Creu i Sant Pau, Catalonia, Spain). The most important determinants observed were patients' beliefs, patient-prescriber relationship, patients' motivation and patient's perception of illness control. (75) All of these factors are modifiable based on a holistic approach including improving patients' information, motivation, skills and communication with his/her health providers among other holistic strategies.

Figure 10: The five dimensions of long-term medication adherence.



Original Image by the World Health Organization (WHO), 2003 (adapted). (69)

In the field of solid organ transplantation, MNA is also considered a very complex and dynamic behavior influenced by several risk factors such as detailed in Textbox 3. MNA determinants should be properly identified and addressed prior to transplant by trained interdisciplinary members of the staff. Historically, research in the solid organ transplant population was focused on the patient-level MNA dimension. (69) Indeed, studies focused their efforts on addressing the patients barriers and intention determinants, which are influenced by patients beliefs: i.e. attitudes, perceived norms or self-efficacy. (76,77)

Textbox 3: Risk factors for MNA in the solid organ transplant population adapted from Fine et al., 2009.

- History of nonadherence
- Psychiatric illness
- Cognitive impairment
- History of abuse
- Substance abuse
- Personality disorders
- Poor social functioning
- Socioeconomic status
- Race/culture
- Adolescence
- Longer illness duration
- Illiteracy
- Poor disease knowledge or insight
- Low conscientiousness
- Low self-efficacy
- Negative beliefs in medications
- Lack of medication knowledge
- No pill box/reminder system
- Medication side effects
- Complex regimen
- Medication cost/co-pay
- Poor access to medication
- Poor social support
- Poor physician communication
- Poor physician–patient relationship
- Poor aftercare/discharge planning
- Poor aftercare/discharge planning

Nevertheless, it is increasingly recognized that recipients are not the solely responsible for medication adherence management post-HTx. (69) In fact, recent research in HTx population, identifies that the non-patient-level factors have a significant weight on adherence to immunosuppressive treatment. (78) Condition-related factors are also relevant and imply these signs and symptoms caused by comorbidities but also side effects or health-related problems derived from immunosuppressive regimen or other chronic drugs. (16) Moreover, a meta-analysis performed by Dew et al. (17) reported that efforts should be directed to deal with provider-related (Textbox 4) and system-related factors (Textbox 5).

Textbox 4: Provider-related factors for MNA in the HTx population. (69,79)

- Failure to recognize MNA.
- Lack of clinical tools to monitoring MNA.
- Prescription of complex regimens.
- Ineffective communication with patients and between prescribers (i.e. Specialists and primary care clinicians).
- Lack of training on adherence management.
- Short consultations.
- Lack of interventions for improving adherence or weak capacity to educate patients among others.

Textbox 5: Health system-related factors for MNA in the HTx population. (69,79)

- Poorly developed health services.
- Lack of resources/support to provide facilities for evidence-based interventions by multidisciplinary teams.
- Co-payments or poor coordinated care between inpatient and outpatient settings.

1.3.4. MEDICATION ADHERENCE ASSESSMENT IN THE SOLID ORGAN TRANSPLANT POPULATION

Medication adherence assessment prior and post-transplant is a mandatory practice in routine care. (14,64,72,76) During regular appointments, clinicians may use clues to identify MNA risk factors like treatment failure, patient not attending to visits, or patient recognizing the difficulties following the regimen prescribed. (64) Validated questionnaires to measure medication adherence in the transplant population are needed to standardize its clinical management and research in this field.

The Spanish HTx quality register does not include medication adherence as a variable of recipient's follow-up. Neither does the national organization (ONT) make recommendations about the methodology or strategies to improve MNA rates. Therefore, there is an increasing need to establish national strategies to measure and to reduce this widespread trend in Spain. Indeed, a national large-scale database may enable a unique opportunity to determine the real impact of MNA in clinical outcomes. The major difficulty in obtaining a common methodology may lie in the fact that there is no perfect medication adherence measure. It is supposed that the combination of the objective and subjective methods can provide a highly sensitive measuring. (71) Nevertheless, recent data suggests that self-reporting and blood assay are reliable methods to be incorporated into a national quality registry. (71) These methods assessed together, may effectively identify high-risk recipients of MNA. (61)

MNA measurement methods are typically classified as direct or indirect. The test, its advantages and disadvantages are detailed in Figure 11. According to direct methods, intaking observation is an impractical practice that could be useful in specific contexts (e.g. psychiatric contexts, children and adolescence or elderly among others). Blood levels assay instead, are mandatory in clinical practice to minimize immunosuppressive variability and has been demonstrated by its correlation with transplant outcomes. (80) However, monitoring drugs is an invasive measure and serves only to assess specific immunosuppressive drugs. Moreover, results may be influenced by the drug's half-life, metabolic rates or drug-drug interactions. (80)

Figure 11: Methods of measuring medication adherence in the solid organ transplant population.

Test	Advantages	Disadvantages
Direct methods		
Directly observed therapy	Most accurate	• Patients can "cheek" pills and then discard them • Impractical for routine use
Measurement of level of drug or metabolite in blood or urine	Objective	• Variations in metabolism • "White-coat adherence" • Expensive
Measurement of biologic marker	Objective	• Requires expensive quantitative assays and collection of samples
Indirect methods		
Patient questionnaires, patient self-reports	Simple, inexpensive	• Susceptible to error with increased time between visits • Results easily distorted by patients
Pill counts	Objective, quantifiable, and easy to perform	• Data easily manipulated by patient
Prescription refill rates	Objective, easy to obtain data	• Does not confirm patients actually took prescribed medications • Requires a closed pharmacy system
Assessment of patient's clinical response	Simple, generally easy to perform	• Factors other than adherence can effect response
Electronic medication monitors	Precise, quantifiable results, easily tracked	• Expensive • Requires return visits and data download • Assumes patient actually takes medication
Measuring physiological markers (eg, blood pressure, heart rate, etc)	Easy to perform	• Marker may be absent for other reason (eg, increased metabolism, poor absorption, lack of response)
Patient diaries	Help to correct for poor recall	• Easily manipulated by patient
Caregiver questionnaire	Simple, objective	• Susceptible to distortion

Image courtesy of Hansen et al., 2007. (56)

With the indirect method, tablet count is a difficult to use method in a clinical outpatient setting because recipients forgot or refuse to bring their packaging. (71) This method has been replaced by the electronic monitoring systems (MEMS), which are often considered the most reliable in drug trials because detailed information is provided on individual medication use with a superior validity. (80) However, MEMS are an expensive method and impractical for screening large populations in clinical practice. (17,56,79) The methodology of using prescription refill records is easy to analyze in practice and this is a relatively inexpensive method. Nevertheless, no information on timing or quantity is provided and large-assessments are limited to data collection or non-networked pharmacies. (57) Subjective methods such as self-reporting, is a simple measure widely used in HTx clinical practice. (17,72) Although patient's self-reports depend on the patient's cognitive abilities and the honesty of replies (56), it has been correlated with objective measures of adherence. (79) Other indirect methods that may be useful

in usual practice, are measuring treatment response, physiological markers such as glycaemia, or patients missing appointments.

The accuracy of the MNA measurement method but also its invasively are also important factors to be taken into account in order to identify the best measure. (Figure 12) It should be noted that while the most objective measures such as blood assay and electronic monitoring can be the most accurate, there are drawbacks that ultimately limit their feasibility. First, these methods require recipients to travel to the clinic, are not universally available and are susceptible to manipulation. (56) Second, using electronic monitoring may not be sure if the patient finally intake medication. Third, the "white coat" is a practice used by some patients to only take immunosuppressive medication properly when the blood assay is coming. (56)

Figure 12: Medication adherence invasive and non-invasive measure methods and their accuracy.

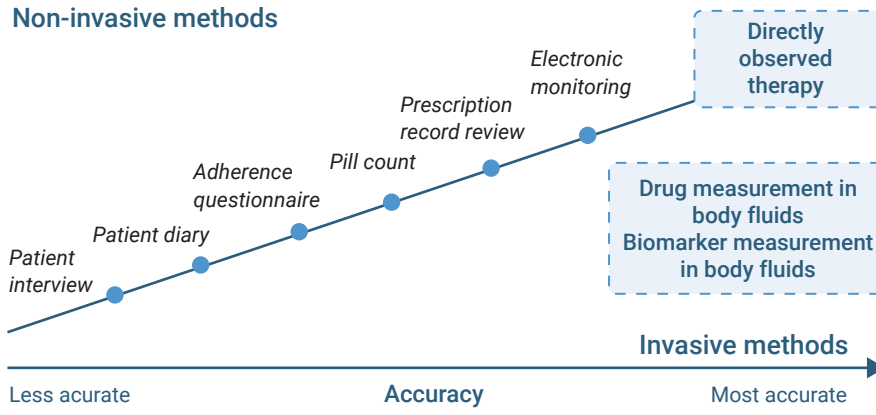


Image courtesy of Vrijens et al., 2017 (adapted). (81)

Therefore, a combination of methods to measure MNA is a highly recommended practice in transplant in-clinics. Indeed, self-reporting (or at least clinicians reporting) and blood assay combined obtained the highest sensitivity (72%) and specificity (42%) when compared with electronic monitoring. (80) The use of this composite adherence score, had demonstrated its

value for screening (i.e. first step) (80) and may be easily implemented in transplant practice. Regarding these two-assessment methods, it is worth further exploring the different implications.

On the one hand, narrow window drugs such as tacrolimus may be affected by intra-patient variability (IPV) in its pharmacokinetics. IPV is defined as the fluctuation in concentrations within an individual patient over a certain period of time during which the tacrolimus dose is unchanged. Variability on exposure may be caused by behavioral factors as MNA, interacting co-medication, food, and genetic factors. Regardless of the cause, an outside level of therapeutic window may lead to a risk of under-exposure and rejection, or toxicity in cases of over-exposure.

The extend on variability of concentrations can be calculated using different methods as the Standard Deviation (SD) or the Coefficient of Variation [CV%=(SD/mean)x100]. This is a more accurate measure than a single drug assay, since it takes into account 3-6 pre-dose concentrations over a period of time. On average, tacrolimus IPV ranges from 15% to 30%. Thus, adherence studies using CV% use to associate IPV with MNA if CV>30% and there is no other cause explaining the high variability. (71,82,83)

On the other hand, self-reporting includes recipient's self-administered questionnaires or the professional's interviews. This method is considered to be the best patient-reported outcome measure (PROM) for the detection of missed doses and erratic timing of medication administration. (56) Also, it is considered an excellent source of information about subjective patient-experiences. (84) Nevertheless, self-reporting usually under-represents MNA because it is prone to recall and because social desirability response bias. (80) Thus, it is imperative to solely use validated self-reporting instruments in this composite MNA measures. (85) A better understanding of patients' subjective reasons of nonadherence in the HTx population its relevant since it can lead to tailored approaches. (18) Therefore, a multi-design of the MNA assessment should include validated questionnaires, but also

qualitative questions adapted to each population particularities are recommended in MNA research.

These adherence scales are administrated typically by a trained provider (i.e. transplant pharmacist, nurse or psychologist) in-clinics setting. The facilities and trained staff time that MNA assessment requires limits the frequency of the measures to a low number of on-site evaluations, usually 3 to 6 months. Nevertheless, MNA is considered a dynamic behavior which could change considerably between assessments, (78) and more frequent self-reported MNA assessment has been related with a better detection of nonadherent recipients. (71) Therefore, feasible and easy to perform instruments and approaches are needed to increase MNA monitoring opportunities. For this purpose, technology tools such as electronic home-based assessment may play a key role in remotely assessing MNA more frequently, and in reducing the need of traditional in-clinic facilities.

1.3.5. MEDICATION ADHERENCE INTERVENTIONS IN THE SOLID ORGAN TRANSPLANT POPULATION

> "Increasing the effectiveness of adherence interventions might have a far greater impact on the health of the population than any improvement in specific medical treatments".
>
> WHO 2003. (69)

Although the impact of medication adherence has been established by the transplant community many years ago (17,65), few efforts have been tailored to reduce MNA. (64) The BRIGHT international study (2015) (72) confirmed that adherence management is increasing. But only a few initiatives were active in HTx centers in 2017. Moreover, no consistent evidence exists that given the strategies used until now in clinical practice, medication adherence can be improved. (57) Thus, innovative already effective-tested strategies should be scaled-up to clinical practice.

As in the case of other chronic populations, there is no unique solution to deal with MNA post-HTx. (77) Given that multifaceted factors affect MNA, (71,79) a multidimensional target of as many risk factors as possible is widely recommended. (77) Levels of intervention on MNA could be classified based on the 5 dimensions of MNA determinants already mentioned above. First, at the *patient-level* including educational/cognitive, counseling/behavioral and psychologic/affective interventions; second, at the *micro-level* regarding patient-provider interactions; third, at the *meso-level* referring to the treatment center or hospital interventions; and finally, at the *macro-level* including healthcare system interventions or within the society where the patient is living.

Typically, intervention studies in chronic illnesses reported small to medium effect sizes of intervention programs around 10%. These studies with limited efficacy, had mainly been based on educational interventions. On the contrary, multi-component behavior modification strategies had demonstrated to effectively improve MNA rates in the transplant population. (56,57) Using these latter techniques, higher effect sizes over 20% could be attained. (73)

Based on a review of the literature, the multilevel goals of any new treatment directed to manage medication adherence should include the already demonstrated effective factors detailed in Textbox 6. These points may be followed by health providers for great applicability on the design of new programs to reduce MNA in the transplant population.

One of these relevant factors frequently underestimated in literature is the expertise of the heart transplant provider. Health providers in charge of assessing risk of nonadherence and delivering interventions to optimize adherence require access to specific training in adherence management. Such training needs to simultaneously address 3 relevant topics such as (i) knowledge, i.e. information on adherence, (ii) thinking, i.e. the clinical decision-making process, and (iii) action, i.e. behavioral tools for health professionals. (69) Furthermore, health professionals' skills and training should be mentioned in manuscripts to enable a better understanding of the role and impact of the team on the results.

Textbox 6: Already demonstrated effective factors to manage medication adherence based on a review of the literature.

- ☑ Identify the best practices to deal with MNA in HTx population and adapt it accordingly to each center context. (64)
- ☑ Identify individual predictors of recipients in need of interventions. (64)
- ☑ Adapt the interventions to be performed in the moment, using the more appropriate tools based on patients' individual matters. (64)
- ☑ Use trained staff on specific transplant MNA risk factors. (69) Multidisciplinary HTx teams should be well-prepared and be proactive. (72)
- ☑ Use behavioral model-linked medication adherence interventions. Behavioral science offers useful theories, models and strategies to design, understand and delivery treatments (interventions). (69,86)
- ☑ Promote communication and counselling. (56,73)
- ☑ Improve convenience of care: simplify medication regimens or facilitating health processes. (56,73)
- ☑ Provide reminders and skills to a better treatment care enhancing recipient's self-monitoring. (56,73)
- ☑ Provide individual behavioral feedback based on intake patterns or goals achieved, goal setting or problem solving. (56,73)
- ☑ Maintain the effect of interventions over a sustained period of time. (68)
- ☑ Establish the intervention on a regular basis. (57,77) Implementation and sustainability should be considered at the design stage to improve the program's long-term efficacy. (70)
- ☑ Base the design of the intervention on relevant standards (i.e. guidelines, experts recommendations, etc.) to be able to scale-up the approach and to provide a meaningful interpretation of the results obtained. (67,70,88,251)

1.3.5.1. Behavior science and medication adherence in the solid organ transplant population

There is growing evidence that in order to maximize the potential of the interventions directed to modify a health behavior, it is necessary to have a theoretical understanding of the behavior change. These behavior theories help health providers (i) to identify the antecedents of the behavior; (ii) to identify the causal determinants of change in a patient or group of patients including cognitive, social and environmental determinants of the behavior; (86) (iii) guide treatments; and also (iv) facilitate the analysis of the effectiveness of the strategy and mediated factors applied. (87,88)

For the purposes of designing a new behavior change intervention, the selection of the adequate techniques is vital. More than ninety behavior theories were identified in health sciences; thus, it is recommended to start with those shown to be effective in the specific area and the target behavior. With this aim, the definition and examples of these techniques are provided in an in-depth review of Michi et al. (2015) for wider use by researchers. (89) The most evidence-based theories in medication adherence are: motivational interviewing, social cognitive theory, health belief model, transtheoretical model, and self-regulation model. Other theories and models reported less often are: cognitive theory, information-behavior-skill model, self-management theory, behavior modification theory or problem-solving theory, among others. (86)

These theories independently reduce MNA with a moderate effect. Possibly because some of these theories are designed to predict behaviors, while others such as motivational interview, are directed to design and deliver intervention strategies. Combining behavior change techniques showed synergistic effects promoting the intervention program efficacy. (86,87) Moreover, motivational interviewing has demonstrated that it could deliver theory-based treatments effectively in the transplant population. (90,91) Which is recognized as a common practice pattern to improve post-transplant medication adherence in HTx centers. (72)

Specifically in HTx population, there is some evidence that behavioral science has been useful since the 1990's. (92,93) Nowadays, experts demand that there is a lack of behavioral intervention programs in this population that should be fulfilled. (61,64,94)

1.3.5.2. Scalability of interventions to deal with medication nonadherence

Based on systematic reviews on interventions in order to improve MNA, (57,95) there is some considerations to take into account in order to develop, implement and generalize to clinical practice a research program. Effectively-based recommendations based on systematic reviews focused on studies to improve MNA are shown in Textbox 7.

Textbox 7: Effectively-based recommendations to develop and implement an intervention in randomized controlled trials (RCTs) based on systematic reviews focused on studies to improve MNA. (57,95)

- ☑ Convenience sample should be avoided. Since nonadherent recipients typically refuse to participate or drop-out during the study, most programs include baseline adherent patients. Thus, the improvement on health outcomes may be clinically irrelevant. For this purpose, all in-clinic patients are recommended to be approached or recommended to be engaged in probabilistic sampling methods.
- ☑ Begin with interventions which already have shown promise or at least not obtained repeatedly negative results.
- ☑ Include direct, indirect methods and composite variables to measure MNA. If self-reported assessments are used, validated questionnaires should be applied, and treatment allocation blinded are recommended to avoid the adherence overestimation bias inherent of indirect measures.

☑ Measure clinical outcomes achieved with the intervention:

(i) Intermediate biological outcomes, i.e. blood pressure or cholesterol.

(ii) PRO as quality of life, knowledge, beliefs, etc.

(iii) Major patient-important clinical endpoints.

☑ Avoid excessive complex interventions. Elaborate strategies to be able to engage MNA sample, thus, simplify questionnaire and procedures.

☑ If effective, the entire intervention should be implementable without excessive additional cost. So, scalable into usual clinical practice procedures should be designed. If it is not possible to scale all the complex interventions, individual components should be tested independently.

Because there is limited information available on how to transfer the results obtained in MNA interventions to wider research or in clinical practice, (86,87) a homogeneous framework is necessary. In this sense, the EMERGE guidelines provided a consensus methodology for interventional studies. (70) Based on these guidelines, the minimum reporting criteria recommended for researchers is summarized in Textbox 8. Reporting this valuable information will help clinicians to understand which techniques proved to be more effective in reducing MNA and why. Regarding the reporting of the conceptual behavioral framework applied in the process of designing interventions, only 18% of the published papers on medication adherence had described it. (86) Nevertheless, this is a relevant criteria since the extent to which specific behavioral theories had been applied to design the interventional strategies has been significantly correlated with intervention effectivity. (96) In this sense, the Theory Coding Scheme (TCS) developed by Michie et al. is a useful checklist and is of great use for researchers in this field to improve interpretation and scalability of the results. (88)

Textbox 8: The minimum reporting criteria recommended for researchers in medication adherence manuscripts according to the EMERGE guidelines. (70)

- ☑ The phases of medication adherence studied must be defined and justified.
- ☑ An operation definition for each medication adherence phase should be included.
- ☑ The instruments used to measure medication adherence (including validity, reliability and other properties) should be specified.
- ☑ The results should be reported for each phase.
- ☑ The conceptual framework for design and developing interventions should be described.
- ☑ A proper classification and description and the exact timing of the techniques used to intervene should be included.
- ☑ If behavioral-based theoretical science has been applied, this should be properly addressed.

In conclusion, there is a lack of theory-based interventional multi-level studies to reduce MNA in the transplant population. New studies should be focused on the health care team and system-level interventions, and not only on patient-level interventions. (77) Further study is needed on the use of modern communication technologies on usual practice and specific roles for allied health professionals such as the clinical pharmacist. (57) The transplant teams have promising effective strategies already available, but also the framework to design them, to implement them and to report quality research intervention programs. As Kirk et al. reported about nonadherence in the transplant population: “It is time for action, not evaluation”. (68)

1.4. THE CLINICAL PHARMACIST ROLE IN THE MULTIDISCIPLINARY TEAM AND TRANSPLANT FIELD

1.4.1. CLINICAL PHARMACY EVOLUTION AND IMPLICATIONS

According to the American College of Clinical Pharmacy (ACCP) "clinical pharmacists are practitioners who provide comprehensive medication management and related care for patients in all health care settings. They are licensed pharmacists with specialized advanced education and training who possess the clinical competencies necessary to practice in team-based, direct patient care environments." For this purpose, "clinical pharmacists work in collaboration with other health providers to deliver comprehensive medication management that optimizes patient outcomes. Care is coordinated among providers and across systems of care as patients". (97)

These patient-centered healthcare services by the clinical pharmacists described by the ACCP showed a significant impact on health outcomes over the last decades. (98) Pharmacist have demonstrated an improvement in patient satisfaction, medication adherence and the use of evidence-based therapies, thereby reducing medication errors and emergency department visits and all causes of readmissions. (99) In addition, they have positively impacted on making significant cost-savings in the most complex populations such as solid organ transplantation. (100,101) Nevertheless, clinical pharmacy should continuously evolve to ensure the seven 'rights' for all drugs provided to inpatients and outpatients in a hospital environment, i.e. right patient, right dose, right route, right time, right drug, right information and right documentation. (102)

The clinical pharmacy movement originated from several factors in the early 1960s in the United States. One of the catalytic factors was that the role of pharmacists on compounding was limited by the pharmaceutical industry's large-scale manufacturing of medicinal products. Likewise, pharmacists' in-

terest in direct patient-care and in the rational use of pharmacotherapy also began growing. The complexity of drug therapy increased; thus, hospitals began to develop specific drug information centers to assist health providers with evaluating medical literature. Moreover, the *unit dose services*, established in the United States in 1964 to improve patient safety, allowed pharmacists to become decentralized on the patient floors. These *unit dose services* derived into *satellite pharmacies* directly allocated into the wards, which were a worldwide opportunity to pharmacists to expand their role out of the Pharmacy Department. In fact, to be nearest to the ward staff increased opportunities for pharmacists to round with the medical team. (102–105) As a result, during the 1980s in the United States, many clinical pharmacists focused their practices in unique medical areas (i.e. specialization) requiring an in-depth specialty training. (104)

Nevertheless, relationships between the pharmacist and the patient were consolidated when the concept of 'pharmaceutical care' was used in 1988 to define the pharmacist's primary responsibility to identify, prevent and resolve drug-related problems. Thereby, the pharmacist began to work directly with the patient to optimize their therapy. Meanwhile the role of the hospital pharmacist was increasing and several research manuscripts were published on the subject of implemented pharmacy practices or research projects, helping to further expand pharmaceutical care. (104)

In Europe, the reality of a clinical pharmacist in hospitals evolved significantly different than in the United States and this was reflected in the current definition of a clinical pharmacist by the European Association of Hospital Pharmacists (EAHP): "Hospital pharmacy is the health care service which comprises the art, practice, and profession of choosing, preparing, storing, compounding and dispensing medicines and medical devices, advising healthcare professionals and patients on their safe, effective and efficient use". (106) Therefore, clinical practice for a European pharmacist is part of the many tasks that this provider is in charge in hospitals. According to an EAHP survey, clinical activities in European hospital pharmacies have not yet been well-documented and their clinical services were not very well im-

plemented until recently. (107) This lack of documentation and a common framework among the countries, made it difficult to extend the spread of clinical practices over the years. (108)

Traditional clinical pharmacy services, such as counseling, immunizations, health screening and medication reconciliation, provided high value to the health systems. (104) Nowadays, new challenges such as managing older patient populations and multiple chronic conditions suggest that the involvement of clinical pharmacists in interdisciplinary care will continue to rise in Europe and worldwide. In order to improve medication safety, efficacy and effectiveness in these complex medical areas, the system demands pharmacists to be extremely well trained supporting the need of a pharmacy specialty-education. (104)

1.4.2. CLINICAL PHARMACY IN SPAIN AND IN THE HOSPITAL DE LA SANTA CREU I SANT PAU

In Spain, the father of the clinical pharmacy has been Dr. Joaquim Bonal, who joined the Hospital de la Santa Creu i Sant Pau Pharmacy Department in 1967. Under Dr. Bonal's charge, the compounding area and the drug information center, were the first valuable services to health providers. These were followed by the first *Drug and Therapeutics Committee* in the country in 1968, whose first task was to elaborate a hospital drugs guide to reach an efficient categorization and selection of the drugs available in the hospital. After that, Dr. Bonal's fellowship in the United States enabled him to explore new practices, subsequently a unit dose service was introduced in 1975. This was followed by the first decentralized oncology pharmacy in 1976 facilitating the pharmacist to engage in doing rounds alongside the clinical team.

A huge impact occurred as a result of these changes, the clinical pharmacy expanded these new practices not only in the Hospital de la Santa Creu i Sant Pau, but also throughout Spain. Meanwhile, at the end of the 1970s, other innovative clinical pharmacy teams were established such as (i) the

Enteral and Parenteral Nutrition Service lead by Dr. Daniel Cardona, and (ii) the Clinical Pharmacokinetics Service in 1984 by Dra. Maria Antònia Mangues, among others. Therefore, the expansion of the pharmacy services continued to guarantee a more secure and effective therapy to patients.

Not only were clinical practices deemed important, but education was also considered to be a high priority to achieve highly qualified trained pharmacists. With this aim in mind, in 1974, Dr. Bonal established the first course in Basic Training in Clinical Pharmacy Practice which continued until his retirement in 1998. Indeed, from that time onwards, two annual meetings of this renowned course are still celebrated each year in Hospital de la Santa Creu i Sant Pau and are directed by Dr. Bonal's successor, Dra. M. Antònia Mangues, with around 110 pharmacists in attendance.

This remarkable history of clinical pharmacy practice in the Hospital de la Santa Creu i Sant Pau, still prevails to the present day across the practice of all pharmacists within the Pharmacy Department and under the direction of Dra. Mangues. The original goals of our Pharmacy Department are constantly being reviewed with the final aim of exploring innovative and integrated approaches which will benefit the patients, their families, the clinical teams and the wider healthcare system.

1.4.3. HOSPITAL PHARMACIST SPECIALITY MODELS

Hospital pharmacists work in an environment in which the most acute patients are in need of tailored and innovative medications management, but also the outpatients setting must deal with high therapeutic complexity derived from multimorbidity. These unique challenges have inspired this thesis work, arising from an actual need to ensure a clinical pharmacist in all Spanish transplant centers.

To be prepared for this demanding environment, most European countries have in place Post Graduate qualifications to raise the skills and competences of clinical pharmacists. (102) The first hospital pharmacy residency in

Spain was established in 1978 and, such as in other large continental countries such as France or Italy, this training is mandatory and can last for a period of 4 years. Europe is currently leading a project to develop a common training framework for hospital pharmacy. This framework will represent an important international agreement on the competencies, knowledge, skills and attitudes required by the profession to be delivered on the 44 European Statements.

The hospital pharmacist's specialization in specific areas, lies in the ability of the pharmacist to provide better care to selected complex groups of patients. In order to provide tailored pharmacy services to patients, families and health providers the pharmacist is required to be highly qualified in the specific medical field. In this sense, the United States pharmacist's specialization is focused on such specialties, thereby enabling these professionals to gain the necessary experience through the completion of a Postgraduate Year 2 (PGY2) in a specific field such as the solid organ transplant residency accredited by the American Society of Health-System Pharmacists (ASHP).

Additionally, a Board of Pharmacy Specialties (BPS) was established in the United States, available worldwide, to certificate an additional level of training in thirteen specialties. In relation to the solid organ transplantation pharmacy board certification, it was recently recognized as a new specialty. This certification is directed at providing evidence-based, patient-centered therapy management and care for patients throughout all phases of solid organ transplantation, at all ages and in various healthcare settings. (109)

1.4.4. THE ROLE OF THE CLINICAL PHARMACIST IN THE SOLID ORGAN TRANSPLANT FIELD

According to the BPS official definition, Solid Organ Transplantation Pharmacists are health providers "specially trained to design, recommend, implement, monitor, and modify pharmacotherapeutic plans to optimize outcomes. They review, analyze, and re-evaluate multifaceted clinical and outcomes data in order to provide quality care and assess program, process, and protocol effectiveness. Finally, they provide education and counseling throughout the transitions of care." (109)

According to the ISHLT international guidelines, transplant centers should strive to have a specialty-trained pharmacist with expertise in pharmacology as part of its multidisciplinary team. Also, these guidelines recommend the role of the clinical pharmacist to support medical providers to follow the demanding task of performing regular screening of immunosuppression complications (i.e. adverse events, minimizing drug doses, drug substitution and drugs withdrawal), the evaluation of new therapies and to develop protocols for HTx recipients. (14)

The specific task of the transplant pharmacist during the pre-, peri- and post-transplant phase has been described by many national organizations, thus uniformizing the practices across the United States (Figure 13). (99,110) A survey performed in 2015 showed the predominant activities performed by pharmacists during the transplant phase and included medication review (95%), lab review (92%), allergy review (88%), medication therapy management (92%), bedside rounds (87%), medication education (79%), documentation (71%), and coordinating discharge medications (58%). Similar activities were reported during the other phases but participation was less common. (111) Nevertheless, according to a national survey performed in 2004, while most transplant pharmacists in the United States spend the majority of their time in clinical practice, they also play a key role in research. (112)

Figure 13: Heart transplant pharmacist responsibilities/standards. (99)

RESPONSIBILITIES/STANDARDS	SOURCE OF STANDARD
Preoperative phase	
Recipient evaluation, education, and documentation of visit	AST
Perioperative phase	
Evaluates, identifies, and solves medication related problems for transplant recipients	UNOS, AST
Educates transplant recipients and their family members on transplant medications and adherence to medication regimen; documentation of visit	UNOS, AST
Acts as a liaison (advocate) between patient and patients' families and other health care team members regarding medication issues	UNOS
Prepares and assists with discharge planning for all transplant recipients; documentation of discharge medication	UNOS, AST
Provides drug information and training for all members and trainees of the transplant team	UNOS, AST
Posttransplantation phase	
Attends daily rounds with prospective evaluation of individual pharrnacotherapy	AST
Communicates all transplant recipient medication issues and concerns to appropriate members of the transplant team	UNOS
Assists with designing, implementing, and monitoring of comprehensive care plans with other team members	UNOS
Coordinates development and implementation of drug therapy protocols, assists in protocol adherence, and measures associated outcomes	AST
Facilitates cost-containment strategies and pharmacotherapy optimization	AST
Quality assurance of medication regimens	UNOS
Clinical research studies	UNOS
Public and professional education	UNOS

Adapted by Milfred-Laforest et al. from the American Society for Transplantation (AST) (113) and the United Network for Organ Sharing (UNOS) (110) statements.

Although the ISHLT position is based on the literature cases of success involving clinical pharmacists, (27,99) these recommendations, unfortunately, are not equally implemented in all countries. The United States is internationally leading the integration of the clinical pharmacist into transplant teams. A survey performed in 2015 in that country confirmed that the involvement of a dedicated transplant pharmacist within multidisciplinary care has become a standard at a large number of centers. With a median of 1.4 pharmacist full-time equivalents (FTEs) (range 0.1-7.1) for every 100 transplants. (111) In Spain, this role had been established by clinical pharmacist experts in the field many years ago (114) but it was implemented solely in a few of the larger centers. Therefore, it is now time to expand the presence of the clinical pharmacist in all transplant teams.

Based on recent practical experience gained by the author during a fellowship in a well-established pharmacy service for the solid organ transplant specialties (the Vanderbilt University Medical Center, Nashville, Tennessee, the United States), and in line with leading experts in the field, there are some notable differences among models in both countries which are limiting the growth of the transplant clinical pharmacy in Spain.

First, in the United States, the number of full-time pharmacists assisting within a particular specialty in the Pharmacy Departments is on the whole much larger. In comparison with most European hospitals, the median number of pharmacists/100 beds is 0.7 (equivalent to 4.5 full-time pharmacists for a 600-bed hospital). These rates would alarm most of the American pharmacists because it entails that European clinical pharmacist are commonly multi-tasking.

Not being dedicated entirely to specific pathologies, acts as major barrier to the integration of the pharmacist in the transplant team's routine i.e. meetings, rounding, etc. Furthermore, it makes less time available to conduct all of the clinical tasks which are expected of the transplant pharmacist in a very demanding population. (115)

Second, the American residency system certifies the pharmacist in a specific specialty enabling them to acquire an in-depth knowledge of the medical area. As a result, this residency program increases work opportunities in that particular field. (99,113,116) Third, the American pharmacy associations have endorsed the transplant pharmacist's role and have promoted it for many years. (113) Recently in Spain, has been created the first official solid organ transplant group in the national hospital pharmacists' association (SEFH) and it is expected that this will help increase this role across the country over the next few years.

Fourth, the American transplant national institutions underpinned the value of the clinical pharmacist in this field. For instance, the American Society for Transplantation (AST) published a White Paper on the recommended roles and optimal training of transplant clinical pharmacists. (113) In addition to

the overwhelming literature supporting the involvement of the pharmacist in organ transplant patient care, the United Network for Organ Sharing (UNOS) bylaws amendment stated that "all transplant programs should identify one or more pharmacists who will be responsible for providing pharmaceutical care to solid organ transplant recipients. The clinical transplant pharmacist should be a designated member of the transplant team and will be assigned primary responsibility for providing comprehensive pharmaceutical care to transplant recipients in a culturally competent manner." (117)

Since these requirements were included in 2004, there has been a dramatic increase in the demand for transplant pharmacists in transplant centers throughout the United States. (116) Thus, funding sources have been significantly increased to support clinical pharmacists coming from national institutions (i.e. Transplant Department, Pharmacy Department or Quality Improvement Department). Indeed, hospitals are not going to be reimbursed if they do not comply with transplant programs requirements. (99) Unfortunately, such inclusive initiatives which are helping to formalize the role of the pharmacist within transplantation in the United States (113), have yet to be implemented in Spain.

In the Hospital de la Santa Creu i Sant Pau, Barcelona, thanks to the legacy left behind by many clinical pharmacists since 1967, the patient-centered clinical care remains at the core of our practice. In each workflow implemented by the Pharmacy Department, a multidisciplinary approach is a key priority to ensure ongoing clinical pharmacy.

Furthermore, the inpatient's most acute care has been always a priority but nowadays the outpatient setting in complex populations is also being recognized as critical for health authorities. Therefore, innovative strategies should be constantly explored to overcome the real limitations mentioned above and to continue raising the profile of the clinical pharmacist in the most complex patients and settings.

In the HTx field, it is highly endorsed that medical providers should not be solely responsible for managing medication adherence and life-style habits

or to tailor complex regimens post-transplant. It has been extensively demonstrated that effective interventions to improve adherence to medications and lifestyle habits requires a multidisciplinary team-based approach.

Therefore, the clinical pharmacist, specialized nurses, social workers and psychologists among other professionals are nowadays working comprehensively to improve health outcomes in the HTx population of the Hospital de la Santa Creu i Sant Pau. Moreover, innovative care models could be applied and directed by the clinical pharmacist with these goals in mind.

1.5. STRATEGIES TO DEAL WITH MULTIMORBIDITY, LIFESTYLE AND MEDICATION MANAGEMENT IN THE HEART TRANSPLANT POPULATION

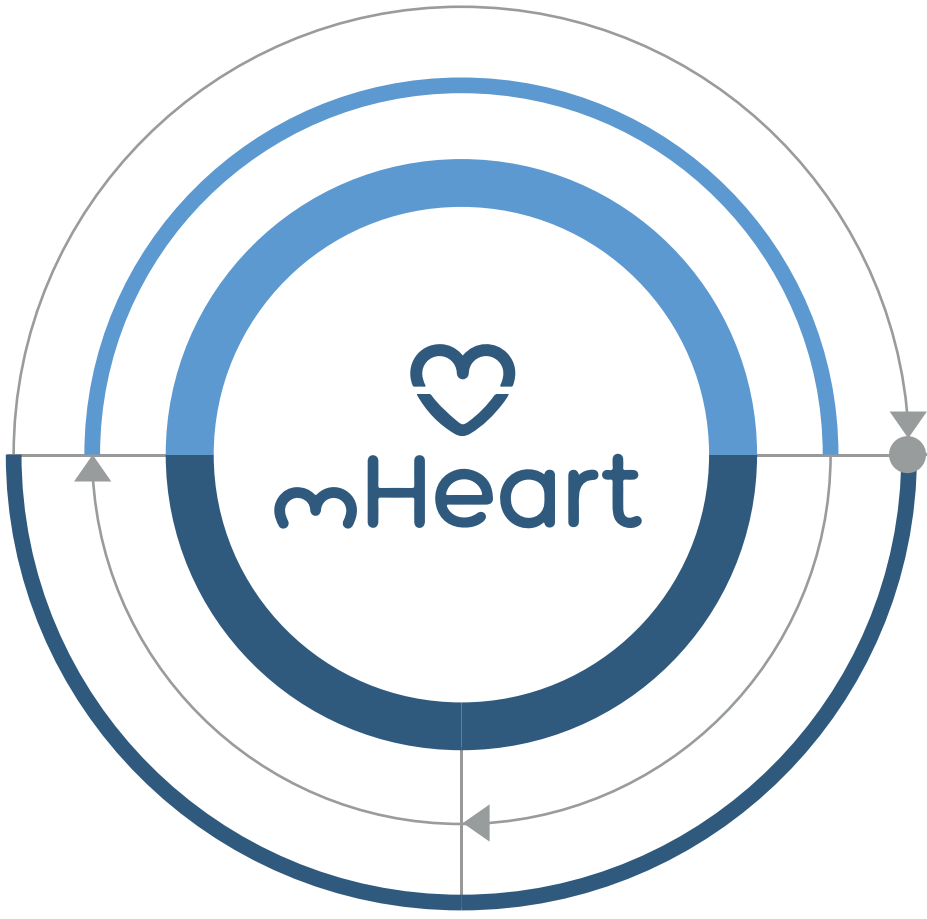
Among chronic patients, it was noticed during the beginning of this thesis, that solid organ transplant recipients characteristically present a greater risk of multimorbidity and therapeutic complexity. In particular, the HTx population has an increased risk of cardiovascular events related with ischemic disease before the transplant but also graft loss related with MNA is life threatening. These findings would justify that HTx is a perfect population to address innovative interventions aimed at improving therapy and disease self-management. If the impact of such interventions in this population is positive, it could provide the first steps to extend the model to other complex diseases across Health Systems.

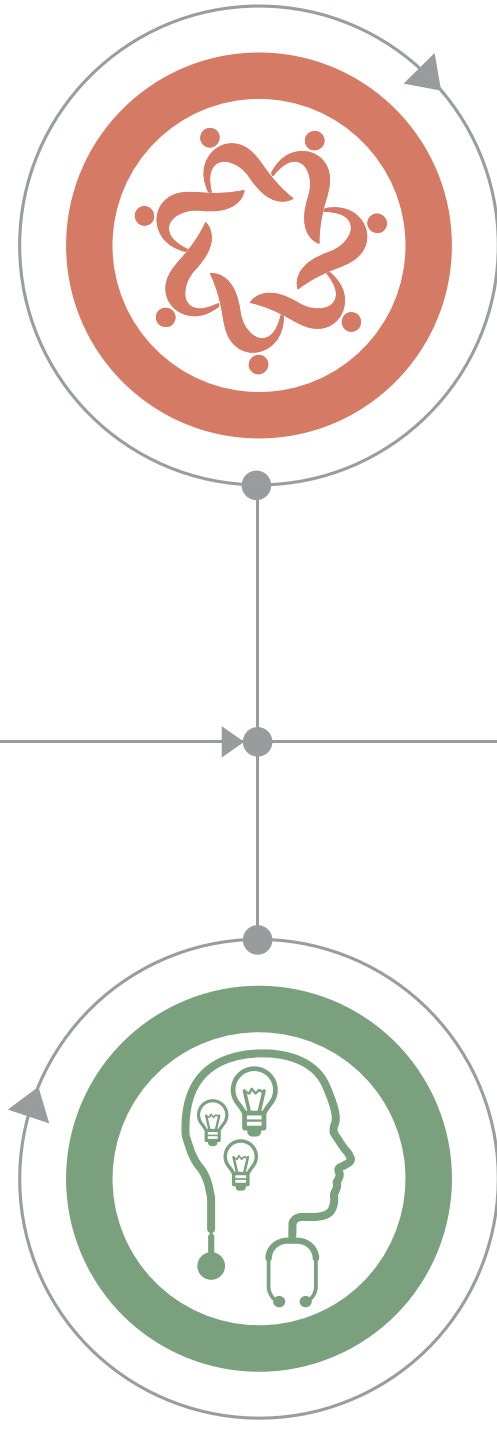
The scarcity of resources often limits the quality of health care in chronic complex patients with polypharmacy in our catchment area. Therefore, an in-depth exploration of successful strategies was necessary to be performed before the design of a new intervention aimed to improve these problems. As a result, specific strategies were selected in terms of their effectivity, feasibility in usual clinical practice, and future scalability to other complex outpatient populations. These strategies are presented in the Context map 1 and were used to design *The mHeart study*.

CONTEXT MAP 1

THE MHEART STUDY STRATEGIES

Strategies to deal with *multimorbidity*, *lifestyle* and *medication management* in the heart transplant population.





STRATEGY 1

Chronic care holistic models

STRATEGY 2

Innovating in clinical practice by mHealth implementation

STRATEGY 3

Behavioral-based multi-level individually-tailored interventions through eHealth

1.5.1. STRATEGY 1. CHRONIC CARE HOLISTIC MODELS

There is emerging evidence that holistic programs in the outpatient setting can have a significant positive effect on medication use, life-styles, service quality and efficiencies. (72,118–120) The chronic illness management (CIM) is a care model which emphasizes continuity of care and promotes self-management support for patients. (121) Applying this model into the transplant follow-up pathways, has shown an improvement in clinical outcomes, reduced healthcare utilization, and reduced costs. (100,122) Moreover, current best clinical practices in the transplant population highlight the need for a partnership between an informed and active patient (77) and a proactive multidisciplinary HTx team. (72) This multidisciplinary team in the transplant field is formed by highly trained health providers delivering comprehensive care and includes a cardiologist, surgeons, nurses, social workers, a psychologist, psychiatrics, and a clinical pharmacist among others.

In particular, making a transplant pharmacist part of the team is an international requirement (121,123,124) in order to provide comprehensive pharmaceutical care to recipients, and strengthens cooperation between families and the transplant team. (113,117) These recommendations are supported by the fact that the Clinical Pharmacy Services showed notable positive impacts in patient health outcomes and is well received by physicians and recipients. (27) Nevertheless, since these results are limited mainly to kidney and liver transplant fields, additional qualitative evidence is required to increase the role of this provider in the HTx population in Spain.

1.5.2. STRATEGY 2. INNOVATING IN CLINICAL PRACTICE BY MHEALTH IMPLEMENTATION

Future innovations in clinical practice as a result of the development and implementation of Internet or electronic-based health technologies (eHealth) may led to many opportunities to implement such chronic care programs in clinical practice. (125–128) The International Society for Research on Internet Interventions (ISRII) is in charge of obtaining the highest quality research and achieving meaningful conclusions from completed studies conducted since 2004. According to this expertise, given the successes of using the eHealth to treat a range of medical and mental health problems, eHealth interventions will play a prominent role in global health. (129) Moreover, a recent report from the European Commission highlights that in eHealth practices priorities are personalized medicine, citizen empowerment and secure access to electronic data. (130)

In particular, mobile device usage in the field of health (mHealth) presents a huge potential for transforming healthcare in the chronic population by increasing the care quality of chronic patients and also helps to reduce costs. (131–135) Among other software functionalities, patient-centered telepharmacy features have succeeded in delivering medication management to patients, in addition to making significant improvements in the supervision of side effects or drug-drug interactions. Furthermore, mHealth has been useful to achieve a more successful monitoring of hypertension or medication adherence. (132–135,137–139)

mHealth presents, therefore, a unique opportunity to support the implementation of a new outpatient healthcare program in the transplant population. (136) Nevertheless, the evidence of such comprehensive mHealth practices on the HTx population is scarce, which highlights a gap in current literature which needs to be addressed as a priority.

Further to the benefits identified above, mHealth generalizability and interactive applications are costly and time-consuming to produce, especially

if they are empirically validated. (129) Moreover, there are several potential barriers when implementing an eHealth-based program in multimorbidity patients' usual care practices, (126) which could lead to the a "dead end" of the clinical program established.

Some of these barriers could be found in Textbox 9. Thus, an integrated strategy to overcome these limitations is critical and should be properly addressed by developers. According to the ISRII experts, the dissemination of these approaches should be also a key priority for developers, and its generalizability ought to be incorporated into the initial design from the outset. (129)

Textbox 9: Potential barriers when implementing an eHealth-based program.

- ☑ Inadequate funding, uncertainty about cost-efficiency.
- ☑ Lack of skill or adequate training of patients and care providers.
- ☑ Resistance by patients and care providers.
- ☑ Inadequate legislative framework.
- ☑ Privacy/security issues.
- ☑ Compatibility between different eHealth tools.
- ☑ Inadequate technical support.

Based on a hypothetically eHealth-based model addressed to HTx population, there are some particular digital features that should be highlighted because of their potential impact on health outcomes:

1.5.2.1. Electronic patient reported outcomes (ePROs)

Electronic instruments to measure patient reported health outcomes (ePROMs) could complement the current standard (140) by introducing the potential of greater screening opportunities for tracking changes at minimal

cost. For instance, in a recent clinical study in outpatients receiving chemotherapy, early detection of patient-reported symptoms via tablet computers showed a significant impact on survival, quality-adjusted survival, and on reducing emergency room visits. (132)

Electronic assessment allows individuals to repeatedly report their own experiences in real time, in real word settings, over time, and across contexts. (141) This type of reporting has the advantage over conventional in-clinic visits and allows the respondent to report their data as it occurs, or very soon thereafter (ideally on the same day). Short recall time frames are preferable because specific behaviors can be recalled using episodic memories rather than generic memories of past events. (141) Another advantage is that electronically collected patient-data provides a unique opportunity to conduct advanced patient-based care planning prior to the visit within the outpatient setting. Having this patient information in advance of the appointment could enable more effective use of the visiting time. Furthermore, it will assist in the prioritization of interventions during the visit, and afterwards may facilitate the documentation of the medical records. (142)

Emerging research indicates that when used for medication adherence measurement, mobile devices produce data of similar quality to that collected by in-clinic self-reporting or by interview. (143) Therefore, it could be of great value to use ePROMs to assess medication adherence without the need for an in-clinic visit thereby also avoiding the interviewer's subjective interpretation of responses. These electronic assessment techniques may limit the major measurement biases of the traditional self-reporting recall data. (144,145)

Furthermore, these techniques can bridge the gap between the accuracy obtained by self-reporting and objective methods. First, the *recall bias* is related to the patient's supra-estimation of medication adherence because of patient's difficulties on recalling a behavior over a long period of time, which may be minimized by shorter recall timeframes. Second, the *social desirability limitation* is the influence of the clinician's or a family member's expectation which may influence the patient's answers during an in-clinic interview. This

bias could be avoided if the patient reports information within a private context and without wider social influences. Third, the *void of contextual information* during an in-clinic interview could be prevented by assessing behaviors within a home-based environment where these behaviors occur.

Additionally, electronic measures provides valuable information to the professionals to implement early and personalized interventions delivered via the Internet. (129,140) The effectiveness of these interventions are based on applying different behavioral change techniques (146) through mHealth features to improve disease management. (141,147) This results in a promising opportunity to enhance recipients' motivation and self-management and leads to improved medication adherence after transplant. (127,136,148)

Nevertheless, the quality of electronic instruments should be properly validated before expanding its use for online purposes. (129) In the case of validated paper and pencil instruments, validity properties related directly to the measurement performances (149,150) should not be assumed to be unchanged in an electronic format. (151) The guidelines of the Scientific Advisory Committee of Medical Outcomes Trust (SAC-MOT), suggest that alternative modes of administration such as electronic instruments should demonstrate the quality of attributes as reliability, validity, responsiveness, interpretability and burden. (152)

1.5.3. STRATEGY 3. BEHAVIORAL-BASED MULTI-LEVEL INDIVIDUALLY-TAILORED INTERVENTIONS THROUGH EHEALTH

Internet-based interventions (also called "electronic interventions" or "eHealth interventions") "are treatments, typically behaviorally based, that are operationalized and transformed for delivery via the Internet" (129) including web and mobile devices. (153) Figure 14 shows a simplified summary of the process of developing a digital intervention according to Muench et al. (154)

Guidelines for the development of interventions (International Society for Research on Internet Interventions (129) and the CONSORT-EHEALTH reporting guidelines (153)) recommended the use of theoretical framework to increase the effectivity of eHealth strategies. Thus, eHealth interventions could use the same rules for health behavior change techniques already mentioned to improve MNA rates using behavioral science. Using models of behavioral change (89) provides a better understanding of the origin of the patient behavior and how the intervention works. Moreover, it increases the eHealth treatments effectivity, (155) and also offers increased comparability and generalizability of successful interventions. (129,153)

Figure 14: Trigger tailoring, engagement planning and ongoing adaptation of the process of developing a digital intervention.

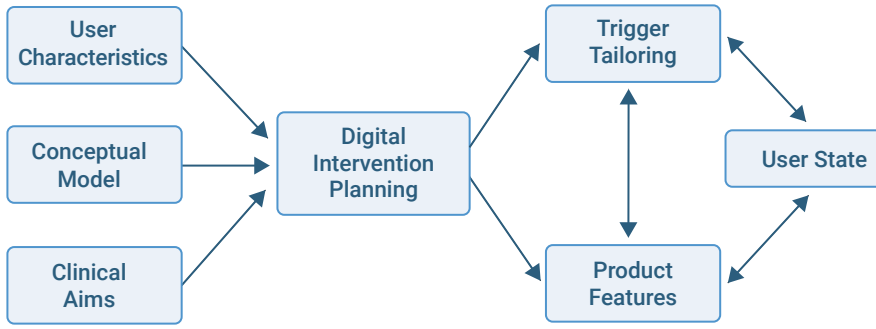


Image courtesy of Muench et al., 2017 (adapted). (154)

Evidence shows that the effectiveness of digital interventions is related with exceeding 60% on the behavioral theoretical design according to the Theory Coding Scheme (TCS). (88) Therefore, it is highly recommended to use these items as a checklist before designing an eHealth intervention in order to ensure that the behavioral theory is being appropriately used. (96) Advocating the use of theory in designing interventions, not only includes a better understanding of the behavior causal determinants (i.e. theoretical mechanisms of change), but also, enables to evaluate the theory effectivity.

Testing this effectivity may lead us to optimize interventions such as abandoning the less useful theories and enabling us to expand the use of more useful ones in clinical practice. (156)

Social cognition theories are based on the premise that patients are rational decision makers who can weigh up the advantage and disadvantages of adopting a behavior. (96) Nevertheless, according to the self-determination theory (SDT), to improve a behavior is imperative to guide the patient to find an autonomous form of motivation and perceiving competence for changing. (157) An eHealth-based approach can be used to provide support for motivating patients' autonomy post-HTx directed to initiating a new behavior, to enhance already achieved motivation or to maintain over-time patient autonomous motivation. The diverse types of support that recipients could receive through an eHealth program are described in Table 3.

Table 3: Examples of support types and techniques for motivating patients' autonomy through an eHealth tool inspired by literature. (78,158)

Support component	Description of the technique for motivating patients' autonomy in the HTx population
Emotional support	Enhancing patient-provider interaction and communication, solving doubts and demands easily from home by message or video call.
Instrumental or practical support	The provision of written information, videos or links to further material to assist in a change behavior easily from any place the patient wants to practice the new skill agreed with the professional.
Informational support	Professionals can perform problem solving techniques using mHealth features to provide patients information when he/she needs or demands it.
Appraisal or affirmational support	Professionals provide to the patient information about their self-management based on ePROMs. This could enhance patient self-evaluation of the progress or completion of a task achieved.

In contrast to non-Internet studies, patient's engagement with an app or website competes with the other events in their daily lives. Thus, motivation to engage with a new behavior could fluctuate in digital studies (129) and requires special attention from developers. In this sense, the presence of human support, such as feedback from providers or personal technical assistance, has been related with higher user engagement with mobile apps and websites and also with the clinical interventions established. (159,160)

Other relevant factors directly related with patients' digital engagement include tailoring intervention delivery and content to users' needs, motivations, and personal characteristics. Tailoring the healthcare recommendations enables users to receive relevant specific personal guidance increasing their impact. (160) Additionally, digital triggers used as behavior stimuli (i.e. alerts, prompts and reminders, notifications, messages, video-calls, feedback, etc.) had also demonstrated enhanced patient adherence to interventions and prevention of attrition. (154,159)

Mobile phones or devices are ideal for providing these human-based tailored digital treatments to people during their everyday lives and in natural settings. Because mobile phones are highly accessible, participants can use them at any convenient time and without intrusion and many people can be reached at minimal cost. (140,161) Furthermore, there is evidence that mHealth interventions can be successfully delivered, are widely accepted by patients, and are effective for treating a variety of health behaviors and physical and psychological symptoms. (141,147)

TIME FOR ACTION IN THE HEART TRANSPLANT POPULATION

2. TIME FOR ACTION IN THE HEART TRANSPLANT POPULATION

In 2014, when the author of this thesis joined the HTx team at the Hospital de la Santa Creu i Sant Pau, post-HTx polypharmacy was higher and medication adherence was lower than expected in this high-risk population. In addition, the intermediate results of the BRIGHT study (an unpublished report mentioned above) showed that recipients' adherence to lifestyle recommendations needed to be embraced by the interdisciplinary HTx team in our setting. Therefore, the HTx population offered an exceptional opportunity to implement a new multidisciplinary holistic outpatient healthcare model to deal with the negative impact of multimorbidity and therapeutic complexity on health outcomes.

With these issues in mind, 4 sequential phases were implemented and abbreviated as *The mHeart Study*. As has been presented in Context map 2, this thesis is the result of the specific goals of these phases, published as consecutive studies. The first phase aimed to quantitatively measure therapeutic complexity by using a validated quantitative index and multimorbidity in chronic-stage HTx recipients. An evaluation of the risk factors for higher therapeutic complexity scores and the association between this complexity and clinical variables post-HTx was also performed. Furthermore, this study also included measurement of the patients' beliefs about their post-HTx medication regimen.

Based on the results obtained in the *first study*, strategies were urgently needed to reduce post-HTx complexity. Therefore, the second phase aimed to develop the mHeart® system (Appendix 1) and to implement an eHealth behavioral-based intervention model to provide healthcare to this complex population in the outpatient setting. Consequently, the study describes the implementation of the model, outlines the facilitators and barriers to the use of mHealth, its benefits, and the willingness to use the model reported by potential users. The design of the intervention model was based on the

above-mentioned standards for the implementation, scaling and assessment of new digital interventions and on a behavioral framework.

The mHeart tool developed is a mobile and web-based software application to support the new comprehensive approach, which seeks to improve therapy management and clinical care. Among other important features, the system included electronic measures to assess health domains such as medication adherence and incorporated digital features to support the pharmacist's behavioral-based interventions and communication components in order to increase patient-provider interactions.

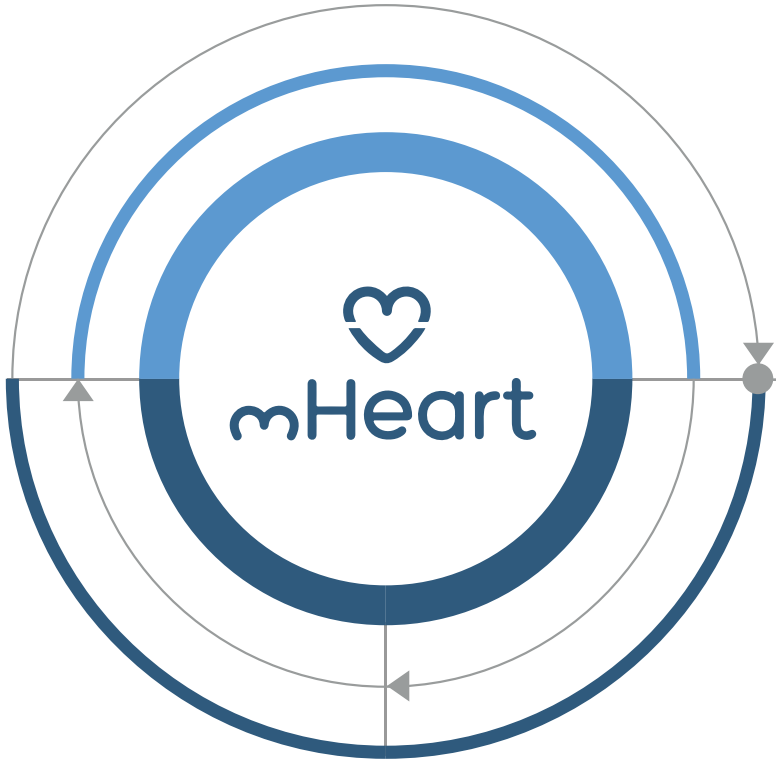
Once the healthcare model and the mHeart tool were ready for clinical use, a *third study* was performed to validate the approach and to support its use in larger research. This was a pilot study in acute-stage HTx recipients to assess the quality of the electronic instruments used to detect nonadherent patients, and the feasibility of *the mHeart strategy* in managing medication nonadherence. *The mHeart strategy* designed consisted of an intensive follow-up program based on individually-tailored digital interventions aiming to change behavior by a pharmacist using the mHeart technology in an interdisciplinary environment. The intervention focused on increasing the opportunities for professional-recipient interactions, and to enhance patient self-empowerment.

Based on the results of the 3 previous stages, the work of this thesis went further to establish the fourth and final stage, the mHeart clinical trial. That study was a long-term randomized clinical trial in chronic-stage HTx patients. The intervention consisted of a long-term mHeart strategy versus a traditional in-clinic follow-up by a multidisciplinary team. The trial aimed to improve recipients' adherence to medication and their experience of their therapeutic regimens. In addition, we explored how mHealth follow-up led to optimization of in-clinic processes in the HTx outpatient setting.

CONTEXT MAP 2

THE MHEART STUDY STAGES AND STUDIES

Four sequential phases were implemented in the heart transplant outpatient setting and abbreviated as *The mHeart Study*. This thesis is the result of the specific goals of these phases, published as consecutive studies.



STAGE 1

Measurement of the multimorbidity and medication complexity in the heart transplant population

STUDY 1

"Multimorbidity and medication complexity: New challenges in heart transplantation"

STAGE 2

Implementation of the innovative mHeart healthcare model

STUDY 2

"Interdisciplinary mobile health model to improve therapy management and clinical care after heart transplantation: An implementation strategy study"

STAGE 3

Validation of the mHeart mobile app and clinical strategy in a pilot study including acute-stage heart transplant recipients

STUDY 3

"The mHeart mobile app to detect medication nonadherence in the heart transplant population: Validation study"

STAGE 4

Testing the impact of the long-term mHeart strategy in a randomized clinical trial in the outpatient heart transplant setting

STUDY 4

"Improving patients' experience and medication adherence after heart transplant using a multilevel mHealth intervention: The mHeart clinical trial"

HYPOTHESIS

3. HYPOTHESIS

The mHeart strategy, a multilevel behavioral-based medication management program using an mHealth tool, will positively impact medication adherence and patients' experience of their therapeutic regimens, as well as clinical practice in the outpatient HTx population

OBJECTIVES

4. OBJECTIVES

The main objective of this thesis was to implement, evaluate and scale in clinical practice a multilevel behavioral change intervention designed to improve medication adherence, patients' experience, and clinical practice by using the mHeart software in the HTx outpatient population.

The specific objectives of each of the sub-studies in this thesis were as follows:

STUDY 1

Multimorbidity and medication complexity: New challenges in heart transplantation

- To quantitatively measure therapeutic complexity using the patient-Medication Regimen Complexity Index Spanish Version (pMRCI-S) and multimorbidity (≥2 comorbidities) in chronic-stage HTx recipients.
- To evaluate risk factors for higher pMRCI-S scores and the association between pMRCI-S and clinical variables post-HTx.

STUDY 2

Interdisciplinary mobile health model to improve therapy management and clinical care after heart transplantation: An implementation strategy study

- To describe the design, testing and implementation of a holistic mHealth model aiming to improve therapy management and clinical care among HTx recipients in an interdisciplinary environment and based on behavioral change interventions.
- To identify user preferences and patients' willingness to use an mHealth approach in our setting.

STUDY 3

The mHeart mobile app to detect medication nonadherence in the heart transplant population: Validation study

- To assess the validity properties of the electronic questionnaires designed to measure medication adherence via the mHeart mobile application in acute-stage HTx recipients versus previously validated traditional on-site questionnaires.
- To explore the feasibility of the behavioral change interventions and clinical workflow performed by a clinical pharmacist through the mHeart tool, and the preliminary effectiveness of *the mHeart strategy* on medication adherence in acute-stage HTx recipients.
- To measure the usability of the mHeart tool by patients and their satisfaction with the mHealth follow-up approach.

STUDY 4

Improving patients' experience and medication adherence after heart transplant using a multilevel mHealth intervention: The mHeart randomized clinical trial

- To assess the impact of *the mHeart strategy*, an intensive behavioral change intervention by a clinical pharmacist using mHealth technology in an interdisciplinary environment, on HTx recipients' medication adherence and patients' experience of their therapeutic regimens.
- To explore the impact of the long-term intervention strategy on optimizing clinical care in the HTx outpatient setting.

METHODS

5. METHODS

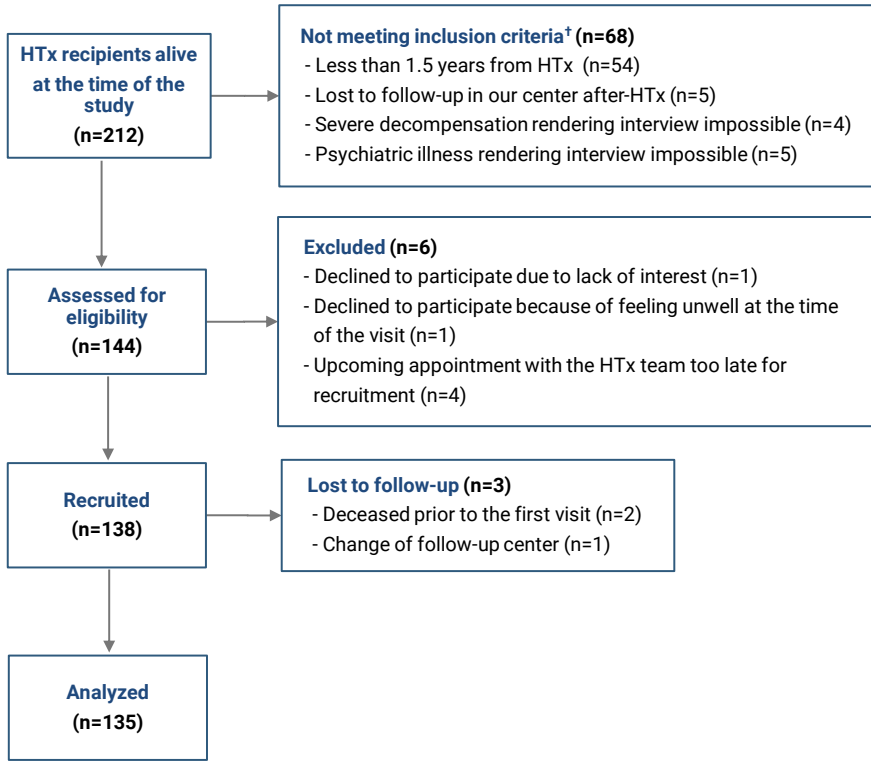
5.1. STUDY 1. MULTIMORBIDITY AND MEDICATION COMPLEXITY: NEW CHALLENGES IN HEART TRANSPLANTATION

5.1.1. STUDY DESIGN AND SAMPLE

This is a single-center, observational study conducted at a tertiary university hospital between October 2015 and January 2017. The study was approved by our internal review board (IIBSP-MHE-2014-55). All patients included in the study gave written informed consent to participate in the study.

Figure 15 shows the flow chart of study participants. We included adult chronic-stage HTx recipients (>1.5 years from HTx) under follow-up in our center and without any reason that would render interviewing impossible.

Figure 15: Flow chart of study participants.



In our study, 94% of the eligible living chronic-stage HTx recipients were included in the analysis (>1.5 years from HTx). A person-to-person interview was needed to obtain essential data. Acute-stage HTx recipients were excluded to focus on the patients' chronic disease complexity. †Inclusion criteria: adult chronic-stage living HTx recipients follow-up in our center, without any reason rendering interview impossible.

5.1.2. DATA COLLECTION

Data was retrospectively collected from the patients' hospital and primary care electronic medical histories and the electronic medication records. To obtain patient-centered data, HTx recipients underwent a face-to-face interview with a transplant pharmacist from April 15, 2014 to April 2, 2015 in the Cardiology Outpatient Clinic. For this purpose, a questionnaire was designed to be completed by the transplant pharmacist during the patient visit. All of the data was recorded in Clinapsis, an Internet-based application for the design and management of epidemiologic and clinical studies. To ensure data accuracy, a medical member of the transplant team and another clinical pharmacist performed a second retrospective review of the patients' electronic health records (EHR) and the data recorded in Clinapsis.

5.1.3. STANDARD PHARMACOLOGICAL REGIMEN

HTx recipients included in this study were treated in accordance with the recommendations of the International Society of Heart and Lung Transplantation. (14) The standard approach to long-term immunosuppressive therapy consists of triple therapy: a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative immunosuppressant (mycophenolate sodium, mycophenolate mofetil, or azathioprine), and low-dose maintenance corticosteroid therapy. Corticosteroid weaning is attempted if there are significant adverse effects and no recent rejection episodes. Other immunosuppressive regimens based on mammalian target of rapamycin inhibitors (everolimus or sirolimus) are used to reduce the onset and progression of cardiac allograft vasculopathy in a small proportion of patients. HTx recipients without intolerance or allergies are treated with lifetime use of aspirin 100 mg daily, calcium/vitamin D, and a statin. Other treatments may be considered depending on comorbidities. (11,14) In this study, medication was classified in 3 categories: 1-*Immunosuppressants*; 2-*Other treatments established in the post-HTx protocol*; 3-*Drugs to treat comorbidities*, including over-the-counter products. (22) Complementary therapies, such as natural plant or homeopathic treatments, were not taken into account. (23)

5.1.4. MEASURES

Multimorbidity measurement

In accordance with Molokhia et al. (162) and Dae Hyun et al. (163) multimorbidity was defined as the presence of ≥2 comorbidities. The category *comorbid disease* included all chronic diagnoses besides the principal diagnosis (i.e. HTx status), lasting 1 year or more, requiring ongoing medical attention, and/or limiting activities of daily living according to the Multiple Chronic Conditions Framework of the U.S. Department of Health & Human Services (2010). Comorbidities were coded according to the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10). (164) Progression of pre- and post-HTx comorbidities were compared.

Therapeutic complexity measurement

Pharmacotherapeutic complexity was measured by applying the pMRCI developed by George et al. (36) in 2004 in a cohort of patients with chronic obstructive pulmonary disease and widely used in different chronic conditions since then. This index was translated, adapted, and validated for the Spanish population (pMRCI-S) in 2016 (22) in 60 patients; 80% of them had >2 chronic comorbidities and were taking a mean of 10 prescribed drugs. The validation results were consistent with the original pMRCI and its subsequent adaptations. The pMRCI-S index has 65 items with different weightings structured in 3 sections: A=*pharmaceutical form*, B=*dosing frequency*, and C=*additional directions* (recommendations given to the patients about taking their medication e.g. to be taken on an empty stomach). The minimum pMRCI-S score for someone on medication is 1.5, corresponding to a single tablet or capsule taken once daily when needed. The pMRCI-S score increases as therapy becomes more complex, with no pre-established maximum value. Each patient's *total pMRCI-S* score was calculated as the sum of the subscores of the 3 medication categories (Figure 16).

Figure 16: Medication categories and drugs according to the HTx protocol in our center.

Therapeutic group 1 Immunosuppressant drugs	**Therapeutic group 2** Treatment associated with HTx	**Therapeutic group 3** Other treatments for comorbidities
☐ Cyclosporine or tacrolimus	☐ Calcium/vitamin D	☐ Antidepressants
☐ Everolimus or sirolimus	☐ Statins	☐ Hypnotics and other drugs for sleep disorder
☐ Prednisone	☐ Aspirin (acetylsalicylic acid)	☐ Antihypertensive drugs
☐ Mycophenolate sodium (MPS) or Mycophenolate mofetil (MMF)		☐ Antiarrhythmic drugs
☐ Azathioprine		☐ Antidiabetic drugs
		☐ Anticoagulants
		☐ Diuretics
		☐ Laxatives and antidiarrheal drugs
		☐ Antiacids
		☐ Pain drugs
		☐ Magnesium or other minerals and vitamins
		☐ Osteoporosis drugs
		☐ Others

Medication post-HTx was classified in 3 medication categories: 1-*Immunosuppressants*; 2-*Other treatments established in the post-HTx protocol*; 3-*Drugs to treat comorbidities*, including over-the-counter products. (22) Complementary therapies, (23) such as natural plant or homeopathic treatments, were not included. According to these categories, the number of drugs prescribed in each category and the pMRCI-S in each category was calculated.

Association analysis measures

Factors predicting higher *total pMRCI-S score* were assessed, including the following variables:

- **Sociodemographic and clinical variables**: gender, age at the time of HTx, age at the time of the study, time from HTx, urgent HTx, heart failure etiology, educational attainment, post-HTx employment status, need for a caregiver, living arrangements, number of hospital

clinicians providing care, use of primary care services, and comorbidities pre and post-HTx.

- **Therapeutic variables**: the total number of prescribed drugs (*total medication count*) and the drug count in each medication category (Figure 16), polypharmacy (defined as >5 drugs), high-risk polypharmacy (defined as >8 drugs (30)). We also included patient-reported outcomes (PROs) as medication adverse effects and 4 qualitative questions created for the study about patient's experience of their medication regimen: (i) patient-perceived inconvenience of medication regimens; and (ii) patient knowledge of the importance of immunosuppressive treatment post-HTx.

The impact of the *total pMRCI-S score* on outcomes was also assessed, including left ventricular ejection fraction (LVEF), cardiac allograft vasculopathy (CAV), malignancy (total, skin and solid) and renal function (creatinine clearance, Cockcroft-Gault formula) at the time of the study. Other outcomes with less than 10 events were removed from the analysis.

5.1.5. STATISTICAL ANALYSIS

Categorical variables are expressed as the number of cases and their percentage, while quantitative variables are expressed as the mean and standard deviation. Nonnormally distributed ordinal or quantitative variables are expressed as the median and quartiles. For the analysis of the association between variables, the Student T test or ANOVA, Pearson correlation, Spearman's rho, chi-square test or Fisher exact test were used when appropriate.

To identify independent predictors of pMRCI-S, we first predicted associations via univariable logistic regression models and linear regression analyses. Variables whose effects suggested associations (i.e. *P*-value<.1) and other clinically meaningful variable (e.g. gender, side effects and drug count categories) underwent multiple regression analysis. A backward elimination method [*P*-value<.05] was used to identify independent predictors of pM-

RCI-S. A logistic or linear regression model was built to evaluate variables associated with outcomes.

The construction of this model required correction for confounding by using inverse probability weighting employing the "ipw" package in R. (165) The model to estimate inverse probability weights contained the following 12 variables: gender, age at the time of the study, age at the time of HTx, total medication count, patients without formal education, patients with disability, the number of medical clinicians involved in patient follow-up, the number of comorbidities post-HTx, need or requirement for caregiver, the number of medication adverse effects, patients lack of awareness of the consequences of not taking immunosuppression, and patients perception of taking excessive medication.

The application of inverse probability treatment weighting (IPTW) during the performance of statistical tests or regression models reduced the impact of confounders. This method is appropriate for binary endpoints when they are scant and prevents overfitting by following the 10-15 events per variable (EPV) rule of thumb. If this EPV rule cannot be satisfied, data reduction is needed (i.e. IPTW). However, when a traditional multivariable adjusted model may be applied, we introduced all relevant variables into the model until the overfit threshold was achieved. Then we were able to compare results and their robustness. The pMRCI-S value best discriminating malignancies and renal function were obtained from the area under the receiver-operator characteristic curve (AUC-ROC) analysis, by Youden's method.

Missing data were imputed using the "mice" package in R (Multivariate Imputation by Chained Equations) whenever necessary (n=1, Multiple imputation if missingness >5%). (166) The statistical analysis was performed with IBM-SPSS (V22.0) and R version 3.5.2 by an independent statistician. The level of significance was <5% (alpha<0.05), bilateral approximation.

5.2. STUDY 2. INTERDISCIPLINARY MOBILE HEALTH MODEL TO IMPROVE THERAPY MANAGEMENT AND CLINICAL CARE AFTER HEART TRANSPLANTATION: AN IMPLEMENTATION STRATEGY STUDY

5.2.1. STUDY DESIGN AND SETTING

This study describes an implementation strategy of a clinical practice improvement model conducted in a Heart Transplant Outpatient Unit of a tertiary university hospital between April 2014 and July 2017. A mixed methods design was applied and included several surveys, interviews, and focus groups. The study was approved by the institutional review board (IIBSP-MHE-2014-55). Participants were adult outpatient HTx recipients, representatives of patient associations, health professionals, providers, and experts in quality, safety or legal fields. Participants were informed of the study objectives and of the team conducting the study. All participants provided written consent.

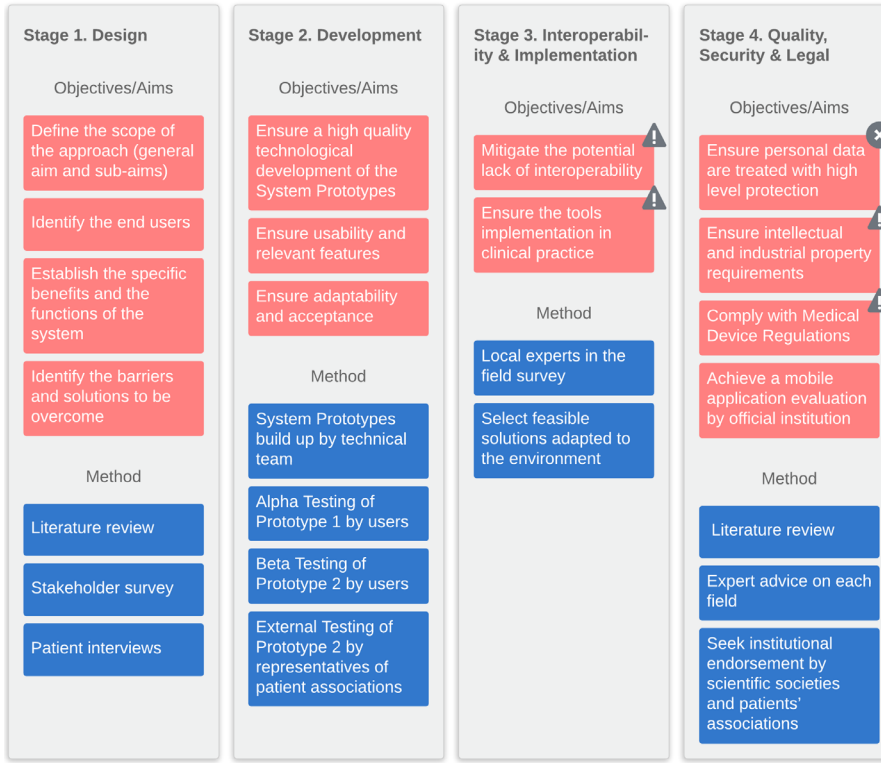
The Standards for Reporting Implementation Studies (StaRI) (167) were followed for transparent and accurate data reporting throughout the study. When the content analysis method was used from group discussions, the consolidated criteria for reporting qualitative research (COREQ) (168) was applied. In addition, the Directions for the International Society for Research on Internet Interventions (ISRII) (129) and the CONSORT-EHEALTH guidelines (153) were followed to report the Internet-based intervention, as appropriate.

5.2.2. PROCEDURES

The mHealth-based model was carried out in 4 stages including design, development, interoperability and implementation, quality, security, and legal requirements. A summary of the aims of the stages and the methodology used is provided in Figure 17. The interdisciplinary clinical team in charge

of the mHeart system was the hospital's scientific advisory team, composed of 4 cardiologists, 2 nurses, 1 psychologist, and 2 pharmacists. All of them were female except 1 male cardiologist. Among the pharmacists, one was a transplant pharmacist with experience in motivational interviewing and transplant therapeutics, while the other had broad experience of clinical pharmacy and managerial skills. The transplant pharmacist was assigned as the scientific coordinator and undertook the following tasks: facilitating procedures and meeting deadlines, prioritizing tasks, liaising with participants and the technical team, and reporting to the scientific advisory team.

Figure 17: Summary of the procedures followed during implementation of the mHeart approach.



A warning sign indicates "plan from the beginning: time and effort consuming". A blade refers to a "mandatory requisite". Definitions: System Prototype (each version of the software developed ready to be tested by end users); Interoperability (properties of systems, eHealth tools and electronic medical records, for data exchange); Users (patients and health providers).

Stage 1. Design

Distinct methodologies were combined to establish the *Stage 1* approach. First, the software was categorized by the scientific advisory team as a behavior intervention technology to facilitate relevant final goals: health behavior change (i.e. increase patients' healthy behaviors and prevent the onset of disease) and targeted disease management (i.e. facilitate therapeutic interventions and improve patients' self-management). The system was initially conceived of as a mHealth software based on a mobile application for HTx recipients in the outpatient setting. The software was interactive with additional human support (i.e. a multidisciplinary HTx team) (129); thus, a website was also designed for providers.

Second, the scientific advisory team reviewed design models for the development of behavior intervention technologies, mainly that of Mohr et al. (169) but also several others, (170–173) which guided how to combine technology engineering with behavioral science. Several expert reports on the efficacy of Internet-based interventions and system engagement were also reviewed. (129,141,147,153,174–177) Behavior change theories were used as a framework to design the interventions and software components. The intervention was based on human support, motivational engagement, and therapeutic alliance. (75,159) The strategies applied included tailored feedback, among others. (86,87,155,156,178) The taxonomy of Abraham and Michie (146) was used to standardize the theory-based interventions in terms of discrete techniques. These techniques are fully described in Appendix 2 to improve the future replication of the approach and its adoption in usual clinical practice or research. Interactive elements were also used as digital triggers to prevent the law of attrition in eHealth interventions (e.g., alerts, prompts, reminders, notifications, messages, and video-calls). (154,159) The components of the system aimed to deliver personalized interventions using motivational interviewing techniques, according to common practice in HTx centers. (72,73)

Third, the scientific advisory team performed a literature review to guide the specific clinical sub-aims and software functionalities that should be priori-

tized in the model (169) and identify the barriers to be overcome. Specifically, institutional reports such as those of the United States Food and Drug Administration, European Union, and Pharmacist Associations statements about eHealth; (131,137,138,179–185) studies on improving polypharmacy and chronic disease management; (128,132–135,139,186,187) and studies or reports describing patient-reported outcome measures with an impact on survival in HTx. (8,11,12,15,16,61,76,187–189)

Fourth, the opinions of end users (i.e. providers and patients) were evaluated. To assess the patients' access to technology and willingness to use mHealth services, the scientific coordinator performed a 45-minute, in-depth, face-to-face interview with each adult chronic-stage (>1.5 years from HTx) recipient included in the study. The recipients were recruited consecutively in the Cardiology Outpatient Clinic. The interviews aimed to determine patients' current access, knowledge and use of technology and their willingness to use an mHealth approach. The interview was based on a questionnaire previously reported by McGillicuddy et al. (190) Sociodemographic and clinical variables were collected from the patients' electronic health records.

To assess the stakeholders' agreement about the gains and barriers associated with an mHealth approach in the HTx population, the scientific coordinator invited a purposive sample of stakeholders to participate in a survey. The themes were previously identified in the literature review and were related with benefits and barriers associated with an mHealth approach directed to multimorbid patients with polypharmacy. The survey was sent by email. The results were used to indicate which clinical sub-aims of the approach should be prioritized, and the software design solutions necessary to overcome the limitations identified. An agreement of >75% of the stakeholders was considered adequate. (191)

The following stakeholders were eligible for selection: interdisciplinary transplant staff (n=21), with no distinction being made in terms of age, knowledge of technologies, or favorable or unfavorable personal opinions about eHealth programs; technology analysts (n=2); experts in mHealth (n=3), i.e.

the Regional Health Department specialist in innovative healthcare projects, the manager of the mHealth.cat Regional Health Department, and the director of the mHealth Competence Center at Mobile World Capital; the hospital manager (n=1); the manager of the Regional Technology, Innovation and Public Health Department (n=1).

Stage 2. Development

Stage 2 aimed to design the technology and test the mHeart. The development of the system was assigned to a healthcare system applications firm. The technical team consisted of 1 analyst, 5 developers (superior systems engineers), 1 designer, and 1 project leader. The scientific coordinator intervened throughout the entire process, providing advice to the technical team and consulting with other providers when necessary. *Development* and *Testing environments* were used by the technical team to respectively produce and consolidate the system prototypes before end users were involved. First, a general software structure was set up (*mHealthCare system*), to then direct it to HTx specifications and obtain the *mHeart* tool. The system was built as 3 applications i.e. Web, Android and iOS mobile applications. To increase the scalability of the approach and data transparency, an in-depth description of the system's technical details, the source code and other relevant details are provided in the online Mendeley dataset. (1)

The mHeart prototypes were tested by end users in a *Staging* environment (Alpha testing), followed by a *Production* environment (Beta testing):

Alpha testing of Prototype 1was performed to explore 3 domains: feature intuitiveness; aesthetics; new software elements or functions not considered during the design stage. With this aim, 2 distinct group sessions were held, one with the hospital's scientific advisory team (n=9), and the other with HTx recipient volunteers consecutively recruited from the Cardiology Outpatient Clinic (n=6). Each session lasted 3 hours and was led by the technical team and the scientific coordinator. A video of the prototype was played to guide the groups through each of the prototype modules and functions. Participants were then asked to complete the same tasks using the

tool on their smartphones. Software usability issues, uncompleted tasks and doubts arising during the sessions were noted. At the end of the session, the 3 domains were explored. Field notes were recorded by a nurse of the scientific advisory team during the session. Conclusions were provided to participants at the end of the session for comments and/or corrections.

Beta testing of Prototype 2 aimed to obtain user feedback simulating a real-world home-based 4-week follow-up. Participants consisted of the scientific advisory team (n=9) and volunteer HTx recipients consecutively recruited from the Cardiology Outpatient Clinic (n=6). Each day, participants electronically completed a data collection sheet with the following domains: technical issues; amendments suggested by the participants; and additional features not included in the prototype. The test findings were analyzed by the scientific coordinator in consensus with the technical team to prioritize tasks.

Additionally, an external session was held in the offices of the local transplant organization. Participants consisted of representatives of patient associations (n=7) recruited via telephone by the organization. The scientific coordinator conducted a 2-hour session with a video demonstration of prototype 2. The participants were then asked to complete the same tasks using the tool on their smartphones. At the end of the session, the domains explored were the tool's acceptance, the adaptability of the approach to other HTx centers, and any new queries or opinions. Field notes were recorded by a nurse of the scientific advisory team during the session. Conclusions were provided to participants at the end for comments and/or corrections.

Stage 3. Interoperability and implementation

Stage 3 aimed to mitigate the potential lack of interoperability (the property of systems, such as mHeart and medical records, to exchange data) and to ensure the implementation of the approach in clinical practice. Themes were identified in advance, including the available technical possibilities and resources to automatically transfer patients' sociodemographic data from electronic health records to mHeart, and to upload data recorded in

mHeart to medical records. Purposive participants were recruited by phone by the scientific coordinator: these participants consisted of the manager of the Hospital Information Analysis Department and the manager of the *mHealth.cat* Regional Health Department. The survey was sent by email on February 16, 2016. The responses were analyzed, and feasible solutions were prioritized by the scientific coordinator in consensus with the technical team.

Stage 4. Quality, security and legal requirements

Stage 4 aimed to ensure the quality and security of the mHealth platform. The scientific coordinator sought the involvement of hospital experts or external consultation on the following domains: data protection and confidentiality policy (n=2), legal requirements (n=2), intellectual and industrial property (n=3) and an external consultant (n=1), and evaluation of mobile apps standards and certifications (n=1). Feasible solutions were applied based on the experts' requirements and technical possibilities. Finally, written endorsement of the quality content was requested from 1 regional health institution, 2 scientific societies, and 2 patient associations.

5.2.3. DATA RECORDING AND STATISTICAL ANALYSIS

To ensure data accuracy, data collected during the study stages were recorded electronically in the online database Clinapsis (192) by a pharmacist. A second review was independently performed by a pharmacist and a physician. None of the data coders were part of the hospital's scientific advisory team.

A statistical analysis was applied to analyze the results of patient interviews and stakeholder surveys. Categorical variables are reported as number and percentage. Quantitative variables are expressed as the mean and standard deviation. Non-normally distributed variables are expressed as the median and interquartile range. The statistical analysis was performed with IBM-SPSS (V22.0).

5.3. STUDY 3. THE MHEART MOBILE APP TO DETECT MEDICATION NONADHERENCE IN THE HEART TRANSPLANT POPULATION: VALIDATION STUDY

5.3.1. STUDY DESIGN AND SETTING

This prospective research study was conducted in the ambulatory setting of a Heart Failure and Transplant Unit of a tertiary university hospital from July 15th, 2016 to December 1st, 2016. The study was approved by the institutional review board of the hospital (IIBSP-MHE-2014-55). Participants were informed of the study purposes, the length of the follow-up, all the procedures, and the investigator team behind the study. Written informed consent was obtained from all participants.

5.3.2. STUDY REPORTING GUIDELINES

The psychometric quality of the ePROMs was based on the Scientific Advisory Committee of the Medical Outcomes Trust (SAC-MOS) (152) and the COSMIN consensus guideline (COnsensus-based Standards for the selection of health Measurement INstruments) (150). The quality of the results obtained was contrasted with the ISOQOL standards (84).

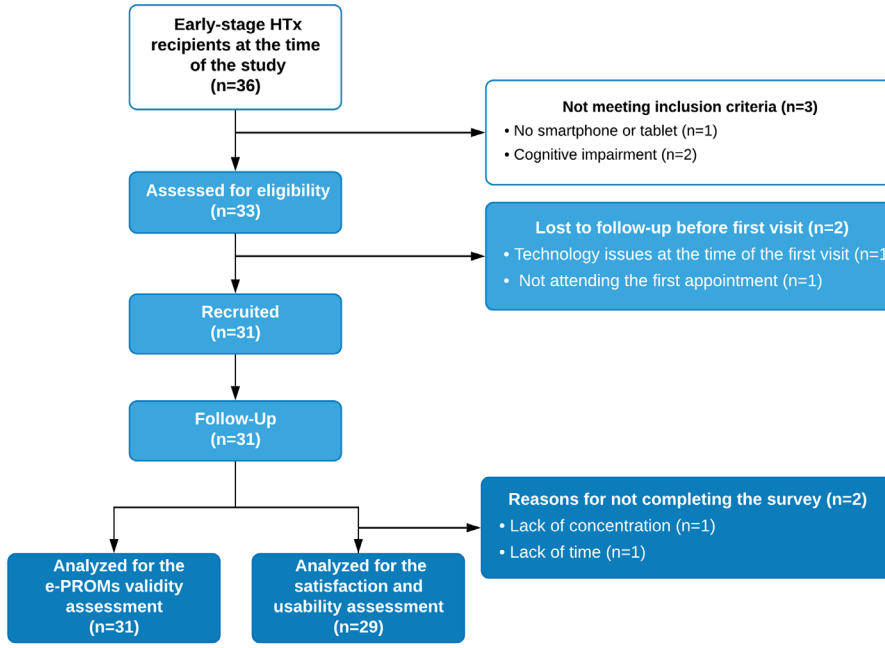
We followed the ESPACOMP (European Society for Patient Adherence, COMpliance, and Persistence) Medication Adherence Reporting Guideline (EMERGE) (70) recommended criteria for transparent and accurate medication adherence reporting data. The directions for the ISRII (129) and the CONSORT-EHEALTH guidelines (section 5) (153) were followed to report the Internet-based intervention program. The Theory Coding Scheme (TCS) (88) provided a reliable method to describe the theory underpinning the interventions.

Additionally, the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) (193) was applied to ensure the quality of reporting of the online satisfaction survey.

5.3.3. SAMPLE

Enrollment was conducted in the Cardiology Outpatient Clinic by transplant physicians during routine in-clinic appointments. All consecutive adult acute-stage HTx recipients (<1.5 years from HTx) owning a smartphone and with no cognitive impairment were included. Cognitive impairment was defined as any condition limiting patients' ability, including memory and thinking skills, to use the mHeart system and complete the questionnaires. No prior computer or smartphone knowledge was required. HTx recipients did not receive any financial compensation, a phone, or wearables for their participation. The patient flowchart is detailed in Figure 18.

Figure 18: Study patient flowchart.



Early-stage, <1.5 years from HTx.

5.3.4. STUDY PROCEDURES

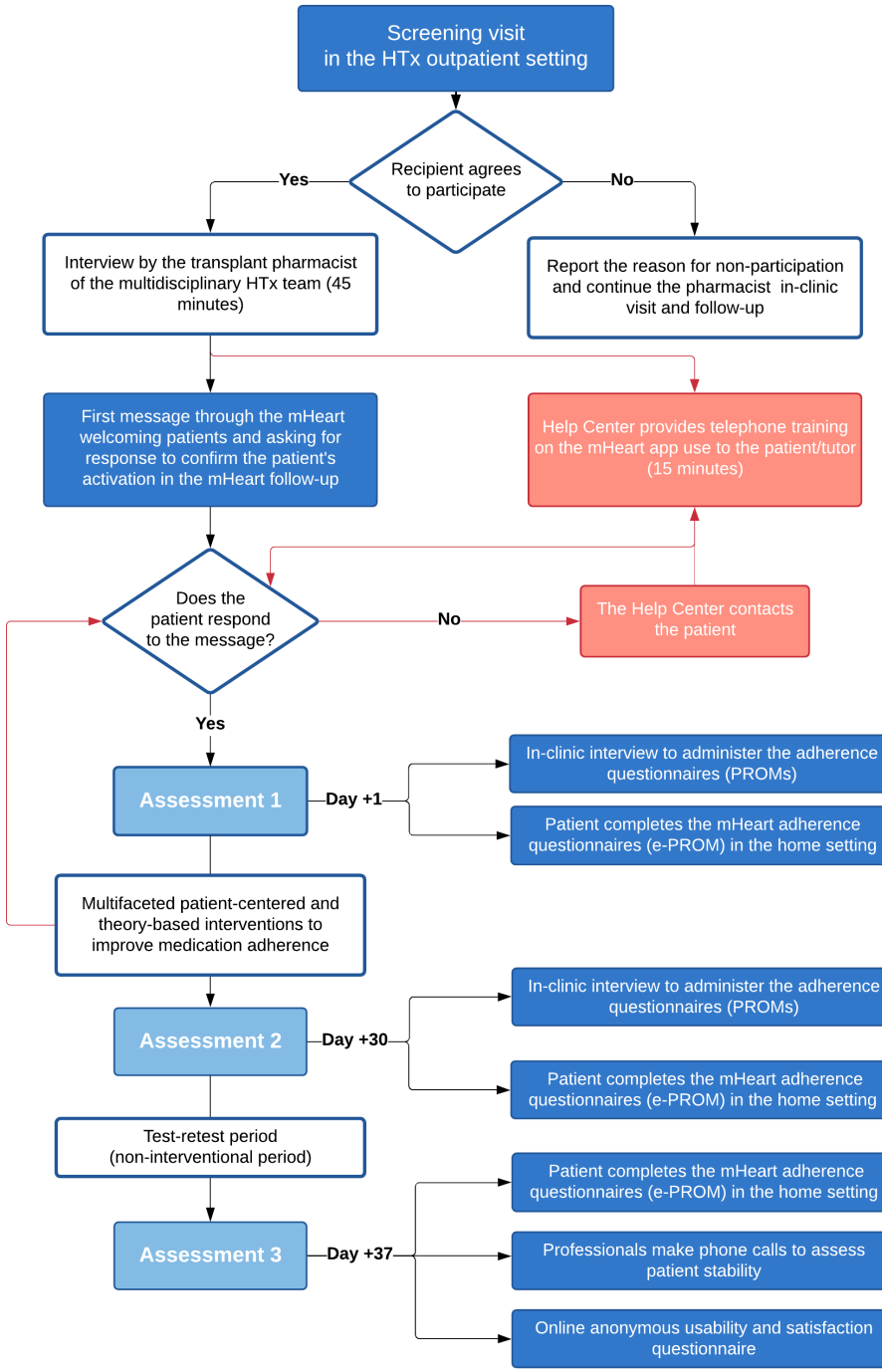
The algorithm summarizing the procedures is shown in Figure 19. After signing the informed consent form, all patients assessed for eligibility (i.e. the same day as enrollment by the physicians) completed a baseline face-to-face visit with the transplant pharmacist followed by an initial mHeart training session.

The interview with the pharmacist lasted approximately 45 minutes. Sociodemographic and clinical data were extracted from patients' electronic health records (EHR). At the end of the visit, the pharmacist registered the new patient's profile in the mHeart system. Patient access was facilitated by an automated message sent to the patient's phone with a username and password.

Next, a technical mHeart initial set-up was provided by the mHeart Help Center of the private firm developing the technology. This session was conducted by telephone and lasted at least 15-minutes to enable at-home monitoring, i.e. (1) downloading the app from the online store, (2) guiding the first access, and (3) providing training on the functionalities of the mHeart platform. This service was also responsible for query resolution and user-assistance throughout the study.

As soon as the patient had received training, the transplant pharmacist sent them a welcome message through mHeart requesting the patients' response to confirm their activation in the mHeart follow-up. Once the patients had responded to this message, 3 consecutive assessments were scheduled. The assessment procedures are described below and were conducted to measure the validity properties of the ePROMs.

Figure 19: Intervention algorithm summarizing the procedures performed throughout the study period.



Assessment 1

After the baseline visit (i.e. on the same day), medication adherence was measured by the pharmacist using in-clinic PROMs. No other interventions were performed to manage medication adherence during this in-clinic interview. The same day, patients were asked to complete the same ePROMs in the home setting using the mHeart tool.

During the 1-month period between assessments 1 and 2, *the mHeart strategy* was applied. Thus, multifaceted theory-based interventions were provided through mHeart to optimize adherence management. (60) The e-interventions were interactive with additional human support from the transplant pharmacist through the mHeart platform. The interventions were individually tailored, based on electronic patient-reported data. Several behavioral change techniques (86,87) were used, based on those with the strongest evidence base in medication adherence such as social cognitive theory, the health belief model, transtheoretical model, and self-regulation model. Less often reported but also used are the information-behavior-skill model (IMB), self-management theory, behavior modification theory, and problem-solving theory, among others. (86) Techniques were based on Michie's taxonomy (146) and were delivered using motivational interviewing (90,91) as a common practice pattern to improve post-transplant medication adherence in HTx centers (72). Interactive elements were also used as digital triggers to prevent the law of attrition; i.e. alerts, prompts, reminders, notifications, messages, logs, reports, visualizations, video-calls, etc. (154,159) The theoretical framework, the behavioral-interventional techniques used, and the interventional workflow are fully described in Appendix 3.

Assessment 2

Once the intervention period finished, and at least 30 days after assessment 1, the pharmacist conducted an in-clinic interview to perform the second medication adherence PROMs assessment. On the same day, the patients were also asked to complete the ePROMs in the home setting.

Thereafter to allow the test-retest reliability analysis, the patients used mHeart for 7 days without any additional interventions by the pharmacist or contact with the HTx team. At the end of the reproducibility time interval the patients were telephoned by the pharmacist to confirm clinical and therapeutic stability.

Assessment 4

After the test-retest reliability analysis, the patients were asked to complete the mHeart ePROMs and the satisfaction and usability survey electronically.

mHeart features used during the study

The mHeart medical device is a home-based mobile phone app complemented by a website. (194) From a technical point of view, access to the tool is multiplatform (i.e. smartphone, tablet, or computer) and can be downloaded for free from online stores. (195,196) mHeart is integrated bi-directionally with the hospital information system (HIS) using encrypted data. This integration between the 2 systems allows mHeart to obtain sociodemographic data directly from the HIS. In addition, mHeart uploads a weekly clinical report to the HIS, including all the data reported by the patients on the platform. The general layout is represented in Figure 20. An in-depth description of the technical specification of the system and the source code are provided in the online Mendeley Dataset. (1) The version number of the app used was 2.7.1 and content was frozen during the study.

From a clinical point of view, the mHeart tool was designed to primarily manage MNA using several features (Table 4). Three of the sub-functionalities of the platform were (i) to resolve patients' queries about their treatment and health condition, (ii) to empower patients in terms of self-care, and (iii) to facilitate professionals' interventions based on patient-reported outcomes (i.e. symptoms and adverse effects to drugs, heart rate, glycemia, weight, and blood pressure). A detailed demonstration of the clinical use of mHeart in the HTx population and more details about functionalities are also provided in the online Mendeley dataset. (1)

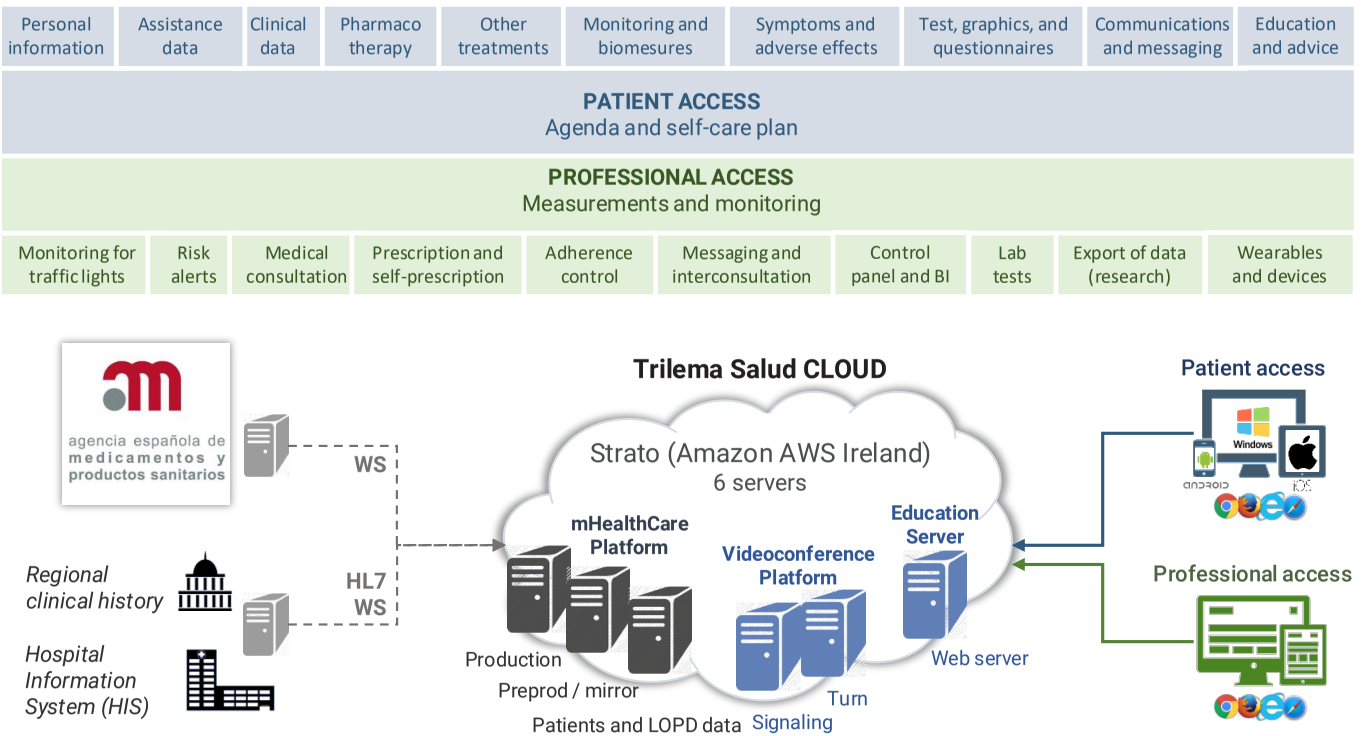


Figure 20: The mHeart Functional Layer and Cloud Architecture

Abbreviations: LOPD, the Spanish Organic Data Protection Law; WS, web server; HL7, High Level-7.

Table 4: mHeart platform features related to medication adherence management.

Patient drug intakes
Push text reminds patients of medication intakes on their mobile phone.
Patients can accept or reject the intakes scheduled. If a patient cancels a dose, they are asked to specify their reason for doing so on a checklist.
Doses taken versus the total number of doses prescribed can be tracked. 1. A traffic light system warns the professional of a decrease in the patient's weekly adherence. 2. Detailed data are presented for patients and professionals in tables or graphically, including reasons for non-taking medication.
Medication adherence ePROMs
The ePROMs included to detect MNA are 1. Haynes-Sackett questionnaire (197,198) adapted to the mHeart platform; 2.The 4-item Morisky-Green-Levine questionnaire. (199)
The professional sets up the frequency of the electronic questionnaire on the patient's diary.
Push text alerts on the phone remind the patient to perform the programmed task.
Test results are shown in tables and graphically to patients and professionals directly from the hospital information system or the mHeart platform website.

Abbreviations: ePROMs, electronic patient-reported outcome measures.

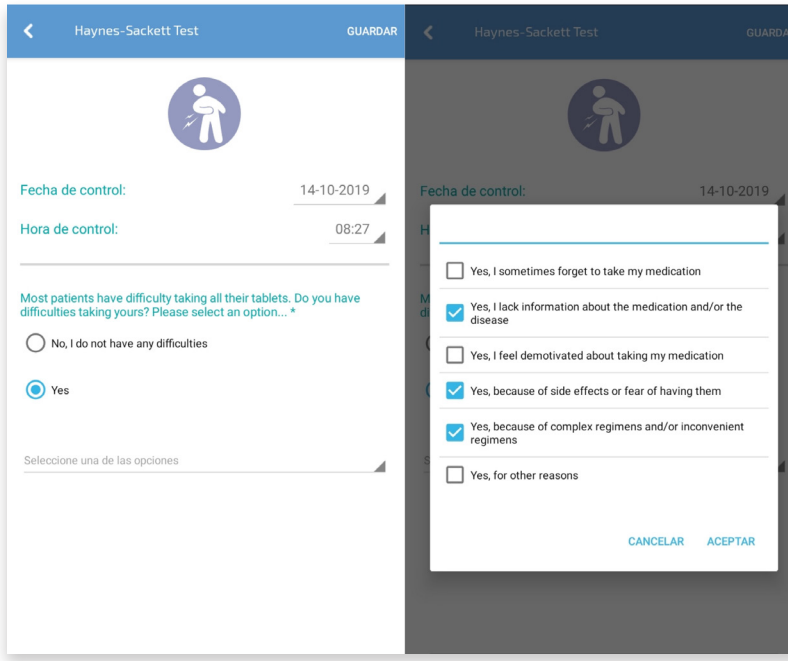
5.3.5. MEASUREMENT VARIABLES

Medication adherence measures

Based on the Ascertaining Barriers to Compliance (ABC) taxonomy, medication adherence is divided in 3 phases: initiation, implementation and persistence. (60) In this study, we focused on assessing the implementation phase of MNA by using self-reported instruments. MNA implementation is defined as "the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen" (i.e. omitting single or consecutive doses, delays in medication intakes, or self-initiated dose changes such as a reduction or increase in dosing). Poor regularity of intakes refers to delays ±2 hours in the transplant population. (71,73) MNA measured by the questionnaires below was defined as any response to items with an answer indicating nonadherence.

The ePROM validity study was based on 2 questionnaires implemented in the mHeart tool. First, the Morisky-Green-Levine questionnaire is a 4-item scale (MMAS-4) (199) assessing patients' medication-taking habits. In transferring the questionnaire to an electronic format, we implemented an exact copy of the Spanish validated version. (200) Second, the Haynes-Sackett questionnaire (197,198) is a 1-item scale asking patients' if they have any difficulty with their treatment. In transferring this questionnaire to an electronic format, we implemented the Spanish version (201) and added 6 multichoice responses on patients' difficulties with medication (202) to improve health providers' understanding of nonadherence (Figure 21). In both mHeart questionnaires, items can be answered using Yes/No check boxes.

Figure 21: Electronic version of the Haynes-Sackett questionnaire including 6 additional responses by patients to aid provider understanding of their difficulties with medication adapted for use with the mHeart platform[a].



[a] The score is based on the item 1 response: No (adherent) or Yes (nonadherent).

For the convergent and discriminant validity assessment, we used the Simplified Medication Adherence Questionnaire (SMAQ) Spanish version as the standard instrument. This questionnaire is a 6-item scale validated in the transplant population taking immunosuppressive treatment. (203) To identify MNA risk factors (79), patients were also asked about (1) knowledge of their regimen; (2) their opinion of the inconvenience of their medication regimens; (3) importance of the immunosuppressive treatment; and (4) adverse effects.

Patient satisfaction and usability measures

Patient satisfaction with the mHeart intervention program and the usability of the tool were assessed by an online non-validated survey created for the study using the Google Forms tool. The survey items consisted of 8 qualitative and 17 semi-quantitative (scored 0-10). No personal information was collected. Adaptive questioning was used to reduce the complexity of the survey. All items had a non-response option. No blank items were allowed. Respondents were able to review and change their answers before submitting their responses.

The survey was closed to the study participants. The participants were sent an mHeart message by a clinical pharmacist different from the transplant pharmacist in charge of the follow-up. The patients had no previous interaction with this provider. The message content consisted of an invitation to complete the opinion survey to help the team and developers to improve the usability and clinical use of the tool. The patients were assigned a random number from 1 to 31. The survey was voluntary, and no incentives were offered for participation. The patients had 1 week to complete the survey before it was closed to new responses. A reminder was sent to all the patients 3 days after the invitation was issued. Patients accessed the survey through a link uploaded in their mHeart personal profile. Survey completion was permitted by the *Google Form* tool when participants provided their identification number to avoid multiple entries.

The responses and the survey completion rate (i.e. ratio of users who finished the survey/users who agreed to participate) (193) were analyzed in depth. The completion time by participants was not determined.

Psychometric variables to assess ePROM validity

The psychometric quality of the ePROMs was assessed in terms of validity, reliability, responsiveness, interpretability, and burden. (150,152) The validation measures and methodology are detailed in Appendix 4 and are briefly described in Table 5.

Table 5: Brief description[a] of the validity properties assessed for the mHeart medication adherence ePROMs.

Content Validity
The inter-rater agreement among an expert panel was performed to assess the following 3 content validity aspects. The expert panel consisted of 14 health professionals including 3 nurses, 7 cardiologists and 4 clinical pharmacists. 1. The suitability of the questionnaires proposed for inclusion in the mHeart app. The discussion was verbal, and voting was by hand. 2. The suitability of the ePROMs compared with the traditional in-clinic version. After written records were taken, a verbal discussion was held. 3. The suitability of the 6 medication difficulties added to the electronic version of the Haynes-Sacket questionnaire. After written records were taken, a verbal discussion was held.
Convergent and Discriminant Validity
1. The correlation between the ePROMs rates with a standard questionnaire was assessed. 2. The complementarity of the adherence to medication domains of the ePROMs included in the mHeart system was measured.
Reliability (reproducibility)
Reliability and reproducibility were assessed using 2 methods with different purposes: 1. The equivalent forms reliability method was used to assess the adequate association between the ePROMs scores and the in-clinic scores. With this aim, the PROMs were assessed in the same group of patients and on the same day. 2. The test-retest reliability method was used to assess the stability of the ePROM scores during a short time period (7 days) in clinically stable patients.

Continued on next page ➔

Responsiveness (sensitivity to change)
Change over time in medication adherence was measured by the difference in ePROM scores while *the mHeart strategy* was performed. A 1-month interval was considered adequate to measure the validity of an indirect smartphone measure. (204,205)
Interpretability
Three aspects were analyzed and discussed: (1) ePROM score interpretation; (2) Meaningful change detected; (3) Scores obtained versus those published by other authors.
Respondent and administrative burden
Several criteriaa were assessed regarding the time, effort, and other criteria of the ePROMs depending on the respondents' and administrative points of view.

[a] Full detail on validity properties assessed is provided in Appendix 4.

Abbreviations: ePROM: electronic patient-reported outcome measure.

5.3.6. STATISTICAL ANALYSES

Descriptive analysis

Categorical variables are expressed as the number of cases and their percentages while quantitative variables are expressed as mean and standard deviation. Ordinal and quantitative variables not showing normal distribution are expressed as the median and quartiles. McNemar's test was used on paired nominal data to determine whether the row and column marginal frequencies were equal. The level of significance was <5% (alfa<.05), bilateral approximation. All analyses were performed using IBM-SPSS (V22.0) and R version 3.5.1.

Validity analysis

The statistical methods used in the validation study are fully detailed in Appendix 4. To estimate the inter-rater agreement measures, an agreement >75% of the expert panel was considered adequate. (191) The one-sample proportions test with continuity correction was applied. Association was measured by the *Phi coefficient* (values range from -1 to +1). Phi values above >0.7 are interpreted as showing a very strong association, 0.4-0.69 as strong, 0.3-0.39 as moderate, 0.2-0.29 as weak, and <0.19-0 as no associa-

tion. (191,206) Agreement was assessed by the *Kappa coefficient* (values range from -1 to +1). Kappa values >0.75 are interpreted as strong agreement, 0.4 to 0.75 indicates moderate agreement, and <0.40 indicates poor agreement. (191,207) In general, values of reliability coefficients above 0.80 indicate excellent agreement. (208)

Sample size

In this finite population of acute-stage HTx recipients, we used a 5 subject-to-variable ratio rule. (209) Therefore, a sample size greater than or equal to 25 participants for a total of 5 items (1-item Haynes-Sackett and 4-item Morisky-Green-Levine questionnaire) was considered the minimum sample required.

To assess validity, reliability (equivalent forms method), responsiveness, interpretability and burden, we included the entire sample in the analysis. For the test-retest reproducibility study, we included HTx recipients who remained stable for 7 days. (210) Stability was defined as the absence of need for medication changes or health center consultation and the absence of any symptoms different from those present at the last clinical evaluation.

5.4. STUDY 4. IMPROVING PATIENTS' EXPERIENCE AND MEDICATION ADHERENCE AFTER HEART TRANSPLANT USING A MULTILEVEL MHEALTH INTERVENTION: THE MHEART RANDOMIZED CLINICAL TRIAL

This single-center randomized controlled trial (RCT) was conducted in the outpatient setting of the Heart Transplant Unit of a tertiary university hospital from July 15th, 2016 to January 31st, 2019. The study was approved by the institutional review board of the hospital (IIBSP-MHE-2014-55) and was registered in Clinicaltrials.gov (ID MHEART: NCT02554578).

5.4.1. PARTICIPANTS AND SETTING

Study participants were adult HTx recipients under follow-up in the outpatient clinic of a tertiary hospital. Exclusion criteria were as follows: (i) patients who were lost to follow-up in our center post-HTx; (ii) patients with a severe decompensation rendering interview impossible (physician-based judgment); (iii) patients with severe cognitive impairment rendering interview or the use of the software impossible (physician-based judgment); (iv) patients with other illnesses such as Parkinson's disease or severe tremor rendering the use of the software impossible; (v) patients not owning a mobile device; (vi) patients living in care centers, limiting their medication self-management; and (vii) chronic-stage patients who acted as volunteers during the technological development of the mHeart mobile application (*alpha* and *beta testing*, *Study 2*). No prior computer or Internet literacy were required. Participants did not receive any financial compensation, or pay for a phone, or wearables for their participation.

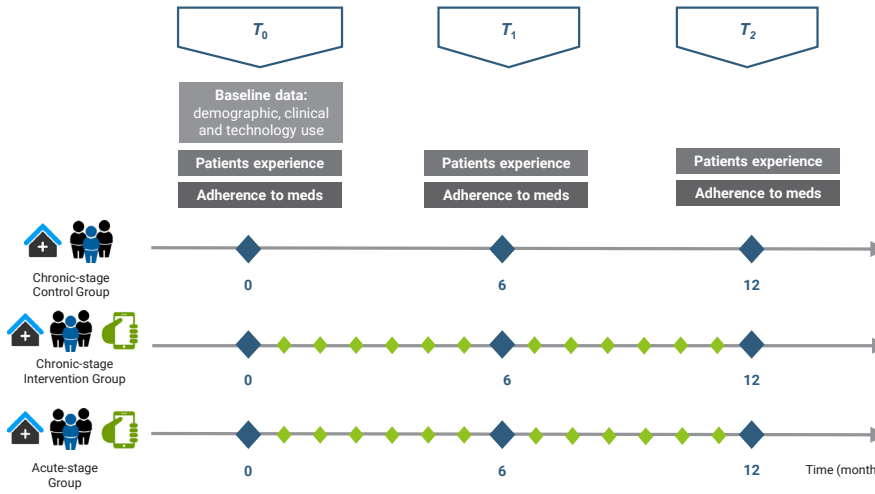
Study participants were recruited from the HTx outpatient clinic. Participants were contacted by telephone by a research assistant prior to study initiation to briefly explain the study and to ask for their agreement to include an additional visit with the clinical pharmacist on the same day as the physician appointment for the chronic-stage recipients (>1.5 years after HTx at the

time of study inclusion). No prior clinical interventions by the pharmacist took place before the first visit. Eligible HTx recipients were consecutively enrolled during their scheduled outpatient clinic visits by the clinical pharmacist. The participants were informed of the study purposes, allocation procedures and the length of the follow-up, all the procedures, and the investigator team behind the study. All patients included in the study gave written informed consent to participate before the baseline visit (T_0) took place.

5.4.2. DESIGN

The study design is shown in Figure 22. Patient allocation during the study period differed depending on the time post-transplant. Chronic-stage recipients (>1.5 years after HTx at the time of study inclusion) were included in the parallel RCT and were randomly assigned 1:1 to the control group (CG) or intervention group (IG). Acute-stage recipients (<1.5 years after HTx at the time of study inclusion) were not included in the controlled trial and were directly offered the same treatment as the IG.

Figure 22: Study design[a].



[a] Face-to-face measurement points are shown as triangles: T_0 (baseline at study inclusion), T_1 (at least 6 months after inclusion), T_2 (at least 12 months after inclusion). The measures assessed during in-clinic visits are shown as squares: baseline information, weaknesses in patients' experience of therapeutic regimens, and medication adherence measures. The treatments are shown as pictograms, i.e. in-clinic outpatient hospital, multidisciplinary team including the pharmacist, and the mHeart mobile application to interact with the pharmacist. The diamonds show the scheduled interaction with the clinical pharmacist: blue (during the scheduled in-clinic visits) and green (through the mHeart tool).

5.4.3. DATA COLLECTION POINTS AND RANDOMIZATION PROCEDURE

There were 3 face-to-face, in-clinic visits spread over 12 months: at inclusion T_0 (baseline visit), T_1 (at least 6 months after inclusion), T_2 (at least 12 months after inclusion). Sociodemographic and clinical data were extracted from patients' electronic health records and in-clinic interviews with the pharmacist. All the data obtained were recorded in Clinapsis (192) by a research assistant not involved in the study. To ensure data accuracy, 1 medical team and 2 clinical pharmacists not involved in the study performed a second review of the patients' electronic health records and Clinapsis data.

The allocation list was sequenced by an independent statistician and sent by email to the Clinical Trial Department of the hospital before study initiation. Randomization was performed after the face-to-face T_0 (baseline visit) was performed. A research assistant asked the Clinical Trial Department of the hospital to perform the randomization. The assistant subsequently recorded the study arm allocation with a patient code in an Excel sheet. The result of the allocation was also reported to the clinical pharmacist, who recorded the result in the patients' electronic health records and informed the participants. Given the nature of the study, it was not possible to blind either the interventionist or the patients.

5.4.4. MEASURES

Demographics and clinical variables

Demographic data were collected at the start of the study (T_0) via an interview using a structured questionnaire. The variables collected are listed in Table 6.

Table 6: Demographic data and clinical information collected.

Demographic information	Treatment measures
Recipient gender (male) Body mass index (kg/m2) Recipient age at the time of the study (years) Patients >75 years old Educational attainment Employment status	Immunosuppressive treatment Total drugs count Patients with polypharmacy (≥8 drugs) Patients with polypharmacy (≥15 drugs) Drugs to treat comorbidities Over-the-counter medicines Complementary therapies
Clinical variables transplant related	**Multimorbidity and use of care levels of the recipients included in the study**
Recipient age at HTx (years) Time from HTx (years) Urgent HTx Heart failure etiology Donor gender (men) Donor age Total ischemia time (min) Mismatch cytomegalovirus (recipient-/donor+) Number of recipients with at least 1 episode of acute cellular rejection episode Number of recipients with at least 1 episode of antibody-mediated rejection Cardiac allograft vasculopathy (CAV) >1 Left ventricular ejection fraction (LVEF %)	Number of comorbidities pre-HTx Number of comorbidities post-HTx Medical clinicians Number of patients who were always visited by the same primary care physician Number of primary care visits in the last month Reasons for primary care visits Number of patients who were always visited by the same pharmacy

Patients' access to technology and willingness to use mHealth services

Patients' access to technology and willingness to use mHealth services were identified at T_0 from a questionnaire based on McGillicuddy et al. (190) asking patients via an interview about (i) technology availability, (ii) Internet access on patients' devices, (iii) frequency of technology use, (iv) Internet usage for health-related purposes, (v) initial assessment of the mHealth approach, (vi) initial assessment of the mHeart® type of platform, (vii) their need for a tutor to hypothetically guide them in the use the platform.

Intervention participants using mHeart were categorized at the end of the study (T_2) regarding their engagement (attrition) with the tool during the study period. Patients were asked if they agreed with the provider's classification and reasons were provided if needed; (i) using mHeart every day (i.e. all messages received by the team were read on time), (ii) using mHeart every day but needed to be reminded to use the mHeart platform at least once during the study period, (iii) not using mHeart every day (and the reason), and (iv) not using mHeart at the end of the study (and the reason).

Patient-experience measures

We measured weaknesses in patients' experience of their therapeutic regimens at T_0, T_1 and T_2 via a face-to-face interview. Based on identified risk factors for MNA, (79) patients were asked to report their (i) self-reliance for medication management; (ii) the perceived inconvenience of their medication regimens (scored 1 to 10); (iii) feeling of taking excessive medication; (iv) opinion about the importance of the immunosuppressive treatment and consequences of not taking it; (v) knowledge of their regimen; and (vi) reported medication adverse effects.

Adherence to medication measures

Based on the Ascertaining Barriers to Compliance (ABC) taxonomy, medication adherence can occur in any of 3 phases: the initiation, implementation, and persistence phases. (60) MNA implementation is defined as "the extent to which a patient's actual dosing corresponds to the prescribed dosing

regimen" (i.e. omitting single or consecutive doses, delays in medication intakes, or self-initiated dose changes such as a reduction or increase in dosing). Poor regularity of intakes refers to delays ±2 hours in the transplant population. (71,73) Non-persistence is defined as early discontinuation. (70) Qualitative and quantitative methods were combined as a mixed design since the dynamics of MNA could be diverse because of the multilevel factors affecting this behavior. (16)

Immunosuppression treatment MNA variables

- ***Self-report***

  Self-reported MNA to immunosuppression was collected at T_0, T_1 and T_2 at a patient interview using the Spanish version of the Simplified Medication Adherence Questionnaire (SMAQ) validated in the transplant population taking immunosuppressive treatment. (203) The SMAQ is a 6-item scale measuring patients' medication-taking habits. A patient is considered to be adherent if he or she responded to question 1=yes and/or 2=no and/or 3=no and/or 4=no and/or 5=never.

  Recipients self-reported the Basel Assessment of Adherence to Immunosuppressive Medications Scale© (BAASIS©) at T_0, T_1 and T_2 via a written version before the in-clinic appointment. The instrument's concurrent validity was demonstrated in kidney (211) and predictive validity (regarding the incidence of late acute rejection) in liver transplant recipients. (212) The instrument measures patients' taking, skipping, timing and dose reduction of immunosuppressive medication. The recall period is limited to 4 weeks. In addition, overall adherence on a visual analog scale (VAS) is scored, ranging from 0 (never took medications as prescribed) to 100 (always took medications as prescribed), with higher VAS scores indicating better medication adherence.

  The Immunosuppressive Medication Timing Scale (IMTS) was measured at T_0, T_1 and T_2 via an interview. The IMTS is a 2-item self-re-

ported non-validated semi-quantitative questionnaire created for the study. We asked the patients in a non-accusatory, information-seeking way about how often they modified the immunosuppressant timetable in the (i) last week and (ii) since the last in-clinic visit. A patient is considered to be adherent if he or she responded No to questions 1 and 2.

- ***Assay***

The tacrolimus and cyclosporine blood levels assay were assessed as part of routine post-HTx follow-up care. Trough blood levels for the drugs were performed using a liquid chromatography tandem mass spectrometry at T_0, T_1 and T_2. No assay is available for azathioprine and prednisone. An assay for mycophenolate mofetil only was measured to rule out toxicity. Sirolimus and everolimus accounted for less than 10 cases. These drugs were therefore not included in this part of the analysis. A therapeutic range for each drug was specified based on the ISHLT guidelines and the protocol of the center and depending on the time since HTx. Independently of the medication regimens and individual target trough blood levels, measured therapeutic ranges were as follows: tacrolimus 0-2 months post-HTx (10-15 ng/ml), 3-6 months post-HTx (8-12 ng/ml), >6 months post-HTx (5-10 ng/ml); cyclosporine 0-1 months post-HTx (250-350 ng/ml), 1-3 months post-HTx (200-350 ng/ml), 3-6 months post-HTx (150-300 ng/ml), and >6 months post-HTx (150-250 ng/ml).

The mean drug level (ng/ml), the coefficient of variation (CV) of drug concentrations [CV%=(SD/μ)x100] and the standard deviation (SD) for each patient were calculated. Variability in immunosuppressive therapy blood levels was assessed as: the number and percentage of patients with therapeutic levels (remaining within the normal range), sub-therapeutic levels (lower than expected target) and supratherapeutic levels (higher than the individual target); the number and percentage of patients with SD>2.5 (interpreted as nonadherence); and the number and percentage of patients with CV%>30% (interpreted

as nonadherence). (71) The analysis was performed for each drug separately (i.e. cyclosporine and tacrolimus) and together.

Co-medication MNA

Via an interview at T_0, T_1 and T_2, we assessed MNA to co-medication using the Haynes-Sackett questionnaire (Spanish version). (201) This is a 1-item scale asking patients the question: "*Most patients have difficulty taking all their tablets, do you have difficulties taking all of yours?*". A patient is considered to be nonadherent if he or she responds affirmatively to the question (1=Yes). This is an easy to perform and open question that helps to continue the interview by asking about how the patient self-manages medication.

Number of missing visits

The number and percentage of patients with missing visits at T_0, T_1 and T_2 were recorded via the retrospective review of the electronic health records.

Composite adherence score

We developed a composite adherence score combining various methods of adherence assessment consisting of the number and percentage of patients with CV<30%, not missing any visits and/or SMAQ score adherent at T_0, T_1 and T_2. If either instrument showed MNA, the patient was classified as nonadherent.

In-clinic personalized interventions by the pharmacist to improve patients' medication management

We recorded person-centered interventions to improve patients' medication management performed during in-clinic appointments at T_0, T_1 and T_2 by the HTx team pharmacist: (i) to check for interactions; (ii) to recommend a pillbox; (iii) to assess pill count at the next in-clinic appointment; (iv) to contact the primary care physician or the pharmacy office; (v) to contact the social worker because of financial problems; (vi) to receive a written regimen timetable; (vii) therapy optimization based on previously published suggested interventions according to the therapeutic complexity observed in our HTx population. (213)

Intensity of the treatment and in-clinic appointments with the clinical pharmacist to perform medication management follow-up at the end of the study

Collateral report

At the end of the study, at T_2, we categorized patients based on their need for face-to-face in-clinic appointments with the clinical pharmacist. The frequency of the follow-up by this provider was also decided. The decision was made in a consensus-based manner between the clinical pharmacist and physicians depending on the level of the patient's self-reliance with regimen management and medication adherence rates.

The following categories were established: (i) no need for regular in-clinic appointments with the clinical pharmacist: discharge from in-clinic visits, discharge with intensive mHeart reminders to track medication adherence, discharge with mHeart reminders to follow lifestyle habits affecting medication regimens; (ii) need for face-to-face in-clinic appointments with the clinical pharmacist: intensive in-clinic follow-up every 6 months, annual in-clinic follow-up to reinforce medication adherence, and annual in-clinic follow-up for other medication-related issues.

5.4.5. STUDY PROCEDURES

All patients

Face-to-face in-clinic interviews with the pharmacist (T_0, T_1 and T_2) lasted approximately 45 minutes and were scheduled for the same day as the physician appointment. During in-clinic appointments, all patients received counseling by the pharmacist about how to improve medication self-management and interventions were implemented (details provided in Measures section). All the data collected, and the interventions conducted were recorded by the pharmacist in the patients' electronic health records. Therapy optimization to reduce therapeutic complexity was also performed after the interview and discussed with physicians including: (i) simplifying the number of doses per day; (ii) reducing frequency; (iii) making administra-

tion requirements easier; (iv) considering non-pharmacologic alternatives; (v) deprescribing chronic treatments or substituting them; (vi) and avoiding a prescribing cascade. These person-centered interventions and case examples to simplify regimens in the transplant population were based on previously designed interventions to deal with the therapeutic complexity observed in our HTx population and are detailed in Appendix 5 (*Study 2*). (213) All the data collected, and the interventions carried out were recorded by the pharmacist in the patients' electronic health records.

Control group

Control group patients received usual care and were asked to attend face-to-face in-clinic interviews with the clinical pharmacist at T_0, T_1 and T_2 to control for attention and attendance bias.

Intervention

Acute-stage recipients and the chronic-stage intervention group received the same treatment as that described for the Control group and an additional mHeart strategy. *The mHeart strategy* consisted of a multilevel medication adherence treatment performed by the clinical pharmacist using asynchronous interactions with patients via the mHeart mobile application features. At the end of the baseline interview after allocation was known (T_0), intervention participants were asked to undergo an initial mHeart training session for 30 minutes in order to: (i) sign the data protection agreement form to use the mHeart platform; (ii) receive verbal and written information about how to set-up and use the mHeart application and website; (iii) receive the mHeart username and code (by a private automated message sent to the patient's phone) after the pharmacist had activated their profile on the mHeart platform; (iv) agree on the scheduled duties of the participant on the mHeart platform according to comorbidities, comedications, and a previous medication management interview.

During the following day, an initial technical mHeart set-up was provided by the mHeart help center of the private firm developing the technology. This session was conducted by telephone and lasted at least 15 minutes

to enable at-home monitoring, i.e. (i) downloading the app from the online store, (ii) guiding the first access, and (iii) providing training on the functionalities of the mHeart platform. This service was also responsible for query resolution and user-assistance throughout the study period. When patients had received the telephone training, the transplant pharmacist sent them a welcome message through mHeart requesting a response to confirm their activation in mHeart follow-up. Once the patients had responded to this message, they were considered activated in the mHeart online follow-up.

Between assessment points T_0 and T_2, multifaceted theory-based interventions were provided through the mHeart tool to optimize therapy management. A detailed description of the design of *the mHeart strategy* to improve medication adherence is fully described in Appendix 2 and 3: the mode of delivery, the theoretical framework, and the features, functionalities and components of the intervention. The workflow adapted for delivery of the intervention has been validated in the validation of *The mHeart Study* (*Study 3*). (214)

Briefly, the e-interventions were interactive with additional human support from the transplant pharmacist through the mHeart platform. The interventions were individually-tailored and mainly asynchronous, based on qualitative feedback from participants during face-to-face in-clinic visits and electronic patient-reported data on mHeart (i.e. medication adherence, symptoms, adverse effects to drugs, heart rate, glycemia, weight, and blood pressure).

Several behavioral change techniques (86,87) were used, based on those with the strongest evidence base in medication adherence such as social cognitive theory, the health belief model, transtheoretical model, and self-regulation model. Less often reported but also used are the information-behavior-skill model (IMB), self-management theory, behavior modification theory, and problem-solving theory, among others. (86) Techniques were based on Michie's taxonomy (146) and were delivered using motivational interviewing (90,91) as a common practice pattern to improve post-transplant medication adherence in HTx centers. (72) Interactive elements were also used as digital triggers to prevent attrition; i.e. alerts, prompts, remin-

ders, notifications, messages, logs, reports, visualizations, video-calls, etc. (154,159)

The development and the quality assurance of the software used in this study (mHeart Version 3) has been detailed previously in *Study 2*. A video in the online Mendeley dataset (1) provides more details about its clinical use and functionalities. The main features of the platform are described in Appendix 6 and aimed (i) to identify MNA recipients, (ii) to resolve patients' queries about their treatment and health condition, (iii) to empower patients in terms of self-care, and (iv) to facilitate professionals' interventions based on online patient-reported outcomes. No downtimes or content changes were made to the system during the study period. Bugs were fixed as needed by the technical team to enhance the usability of the platform by recipients.

5.4.6. STUDY REPORTING GUIDELINES

We followed the recommended criteria of the ESPACOMP (European Society for Patient Adherence, COMpliance, and Persistence) Medication Adherence Reporting Guideline (EMERGE) (70) for transparent and accurate reporting of data on medication adherence. The directions of the ISRII (129) and the CONSORT-EHEALTH guidelines (153) were followed to report the mobile-based intervention and the RCT. The Theory Coding Scheme (TCS) (88) provided a reliable method to describe the theory underpinning the interventions.

5.4.7. POWER CALCULATION

Based on an unpublished report of our center sent to us by the BRIGHT international study, (15) the baseline medication adherence rate in our HTx population was 67%. Therefore, the sample size was calculated to detect a difference in adherence measured with the SMAQ scale between T_0 and T_2 of at least 25%. The statistical power was 80% using a 2-tailed test run at an alpha level of .05. The resulting sample size was 136 patients (1:1 allocation) including dropouts or losses to follow-up (estimating at least a 10% loss).

5.4.8. STATISTICAL ANALYSIS

The statistical analyses for the acute-stage group and the RCT chronic-stage group were performed separately. For descriptive statistics, categorical variables are expressed as the number of cases (N) and their percentage (%), while quantitative variables are expressed as the mean (M) and standard deviation (SD). Nonnormally distributed ordinal or quantitative variables are expressed as the median (ME) and quartiles 25-50-75 (IQR).

The contrast analysis among the RCT intervention and the control group was performed, as well as the improvement in each study group at times between T_0 and T_2. The analysis included parametric tests (t-test) and non-parametric tests (Mann-Whitney) for continuous variables (depending on the normality of the distribution, the Kolmogorov-Smirnov or Shapiro-Wilk test was used) and chi-square tests or Fisher's exact test, as appropriate, for the remaining categorical variables.

The results of comparisons are described by odds ratios (OR) with their corresponding 95% confidence interval (95%CI) for categorical variables or the magnitude of the difference for quantitative variables, as well as the statistical significance (*P*-value) of the difference. OR were not calculated for polychotomous variables (those with more than 2 distinct categories).

For all analyses, statistical significance was set at 5% ($\alpha<0.05$) with 80% power ($\beta=0.20$). All statistical tests were 2-tailed. Missing values were not imputed nor were anomalous values substituted. For some values, although the between-group differences were significant [*P*-value>.05], OR and 95%CI could not be calculated due to the lack of information on one or more of the categories of the variable (zero cases). In these cases, the magnitude of the difference and its precision are unknown.

The statistical analysis was performed with IBM-SPSS (V25.0) and R version 3.5.2 by an independent statistician.

RESULTS

6. RESULTS

6.1. STUDY 1. MULTIMORBIDITY AND MEDICATION COMPLEXITY: NEW CHALLENGES IN HEART TRANSPLANTATION

6.1.1. DEMOGRAPHIC INFORMATION

A total of 135 chronic-stage HTx recipients were included (Figure 18). The patients' demographic and clinical characteristics are summarized in Table 7. Mean age was 57 (SD14) years; 31% were women. The mean time from HTx was 12 (SD7, range 2-31) and was ≥15 years in 32% of the recipients. As many as 21% of the patients needed a caregiver, and 24% were currently employed.

Table 7: Demographic and clinical characteristics of the HTx recipients included in the study.

Variables	N=135
Recipient gender (women), n(%)	41 (31)
Recipient age at the time of the study, years±SD ▪ Patients >75 years old, n(%)	57±14 5 (4)
Recipient age at HTx, years±SD	45±16
Donor age, years±SD Donor gender (men), n(%)	35±14 69 (51)
Time from HTx, years±SD ▪ >1.5-3; 3-5; 5-10; 10-15, n(%) ▪ ≥15, n(%)	12±7 (2-31) 11 (8); 16 (12); 27 (20); 37 (28) 43 (32)
Body mass index, kg/m2±SD	27±6
Mismatch CMV (recipient-/donor+), n(%)	17 (13)
Heart failure etiology, n(%) ▪ Congenital ▪ Coronary/ischemic ▪ Myocarditis ▪ Cardiomyopathy ▪ Valvular cardiac disease ▪ Hypertrophic cardiomyopathy ▪ Re-transplant ▪ Other	 7 (5) 36 (26) 5 (4) 58 (43) 9 (7) 8 (6) 4 (3) 5 (4)

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Variables	N=135
Urgent HTx, n(%)	33 (24)
Total ischemia time, min±SD	189±58
Number of patients with at least 1 episode of ARE, n(%)	5 (4)
AMR, n(%)	1 (1)
CAV, n(%)	69 (51)
LVEF, %±SD	66±8
Immunosuppressive treatment, n(%)	
▪ Cyclosporine	31 (23)
▪ Tacrolimus	100 (75)
▪ Everolimus	20 (15)
▪ Sirolimus	3 (2)
▪ Azathioprine	4 (3)
▪ Mycophenolate (MPA)	99 (74)
▪ Corticosteroids	114 (86)
Chronic treatments according to the HTx protocol, n(%)	
▪ Acetylsalicylic acid (aspirin)	80 (61)
▪ Calcium/vitamin D	52 (39)
▪ Statin	114 (86)
Educational attainment, n(%)	
▪ No schooling	15 (11)
▪ Middle school graduate	58 (43)
▪ High school graduate	25 (19)
▪ University graduate	36 (27)
Employment status, n(%)	
▪ Disability	74 (55)
▪ Retired	20 (15)
▪ No previous employment activity	7 (5)
▪ Currently employed	33 (24)
Need or requirement for caregiver, n(%)	28 (21)
Lives with someone else, n(%)	115 (88)

Abbreviations: AMR, antibody-mediated rejection; ARE, acute cellular rejection episode; BMI, body mass index; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; HTx, heart transplantation; LVEF, left ventricular ejection fraction; SD, standard deviation.

6.1.2. PREVALENCE OF MULTIMORBIDITY

Data on multimorbidity are detailed in Table 8. Multimorbidity was present in 95% of the patients. The mean number of comorbidities was significantly higher post-HTx than pre-HTx [6 (SD3) versus 2 (SD2), *P*-value<.001]. The co-morbidity count did not vary with longer time post-HTx [r=0.061; *P*-value=.49].

Table 8: Multimorbidity and use of care levels of the HTx recipients included in the study.

Variables	N=135	
Number of comorbidities		
▪ Pre-HTx, mean±SD (range)	2±2 (0-10)	
▪ Post-HTx, mean±SD (range)	6±3 (0-11)	
▪ Post-HTx >2 comorbidities, n(%)	128 (95)	
Correlation between comorbidities count post-HTx and:		
▪ Number of comorbidities pre-HTx	*P*-value<.001	
▪ Time from HTx	r=0.06, *P*-value=.49	
Patients with comorbidity, n(%)	**Post-HTx**	**Pre-HTx**
▪ High blood pressure	94 (70)	31(23)
▪ Dyslipidemia	73 (54)	28 (21)
▪ Chronic kidney failure	58 (50)	28 (21)
▪ Osteopathies and chondroplasties	52 (39)	12 (9)
▪ Diseases of the nervous system	51 (38)	19 (14)
▪ Mood and anxiety disorders	49 (36)	24 (18)
▪ Digestive system diseases or disorders	42 (31)	19 (14)
▪ Diabetes mellitus	42 (31)	14 (10)
▪ Neoplasia	39 (29)	8 (6)
▪ Arthropathies	27 (20)	7 (5)
Medical clinicians (other than the transplant team)		
▪ Mean±SD (range)	3±2 (0-9)	
▪ 0; 1-2; 3-4; >5 clinicians, n(%)	18 (13); 38 (28); 56 (42); 23 (17)	
Types of medical clinician, n(%)		
▪ Dermatologist	48 (36)	
▪ Nephrologist	42 (31)	
▪ Rheumatologist	18 (13)	
▪ Orthopedic surgeon	16 (12)	
▪ Endocrinologist	15 (11)	
Number of patients who were always visited by the same primary care physician, n(%)	122 (90)	
Number of primary care visits in the last month, n(%)		
▪ None; 1-2 visits; >3 visits	82 (61); 50 (37); 2 (2)	
Reasons for primary care visits, n(%)		
▪ Medical consultation	66 (52)	
▪ Refill prescriptions	61 (48)	

The most prevalent new-onset comorbidities recorded after HTx were hypertension (47%), dyslipidemia (33%), osteopathies and chondropathies (30%), and renal failure (29%). These comorbidities were treated by 3 (SD2, range 0-9) non-cardiologist medical clinicians, mainly dermatologists (36%) and nephrologists (31%). Nearly half (48%) of the patients visited only their primary care physician to refill prescriptions.

6.1.3. PREVALENCE AND DESCRIPTION OF THERAPEUTIC COMPLEXITY

Treatment complexity is summarized in Table 9. The mean *total medication count* was 12 (SD3, range 5-21). *Drugs to treat comorbidities* accounted for 58% of the total count (Figure 23). All patients had polypharmacy. The mean *total pMRCI-S score* was 42 (SD11, range 20-84). Of this total, *drugs to treat comorbidities* accounted for 45% followed by *immunosuppression* (42%) (Figure 23). Of the pMRCI-S subsections, a*dditional instructions* for treatment accounted for 49% of the *total pMRCI-S score*, and *dosing frequency* for 33% (Figure 24).

Table 9: Therapeutic complexity of the HTx recipients included in the study.

Variables	N=135
Total drugs count, mean±SD (range) Q1:Q2:Q3	12±3 (5-21) 9;11;14
Patients with polypharmacy (≥5 drugs) n(%) ▪ ≥8 drugs n(%)	135 (100) 120 (89)
Medication categories count, mean±SD (range) Q1:Q2:Q3 [% of total] ▪ 1. Immunosuppressants ▪ 2. Other drugs established in HTx protocol ▪ 3. Comorbidities treatments	 3±0.4 (2-4) 3;3;3 [24] 2±1 (0-3) 1;2;3 [17] 7±3 (1-17) 5;7;9 [58]
Total pMRCI-S score, mean±SD (range) Q1:Q2:Q3	42±11 (20-84) 34;40;47
pMRCI-S sections; mean±SD (range) [% of total score] ▪ Section A. Dosage form ▪ Section B. Dosing frequency ▪ Section C. Additional instructions	 7±4 (2-20) [18] 14±4 (5-29) [33] 21±6 (11-40) [49]

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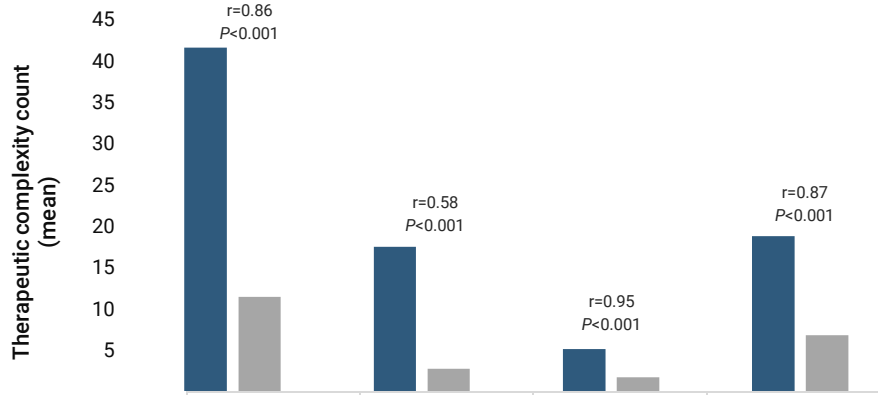
Variables	N=135
pMRCI-S medication categories; mean±SD (range) [% of total score]	
▪ 1. Immunosuppressants	18±3 (10-25) [42]
▪ 2. Other drugs established in HTx protocol	5±2 (0-10) [13]
▪ 3. Comorbidities treatment	19±11 (1-57) [45]
Immunosuppressants pMRCI-S, mean±SD [% of total score]	
▪ Section A. Dosage form	1±0.2 [6]
▪ Section B. Dosing frequency	5±1 [28]
▪ Section C. Additional directions	12±2 [66]
Drugs HTx-related pMRCI-S, mean±SD [% of total score]	
▪ Section A. Dosage form	1.8±1 [35]
▪ Section B. Dosing frequency	1.9±0.9 [37]
▪ Section C. Additional directions	1.5±0.7 [29]
Comorbidities drugs pMRCI-S, mean±SD [% of total score]	
▪ Section A. Dosage form	5±3 [24]
▪ Section B. Dosing frequency	7±4 [38]
▪ Section C. Additional directions	7±5 [39]

Abbreviations: HTx, heart transplant; Q1:Q2:Q3, lower, middle and upper quartiles; pMRCI-S, patient Medication Regimen Complexity Index Spanish version; SD, standard deviation.

Figure 23: Therapeutic complexity according to the pMRCI-S score and the drugs count grouped into medication categories[a].

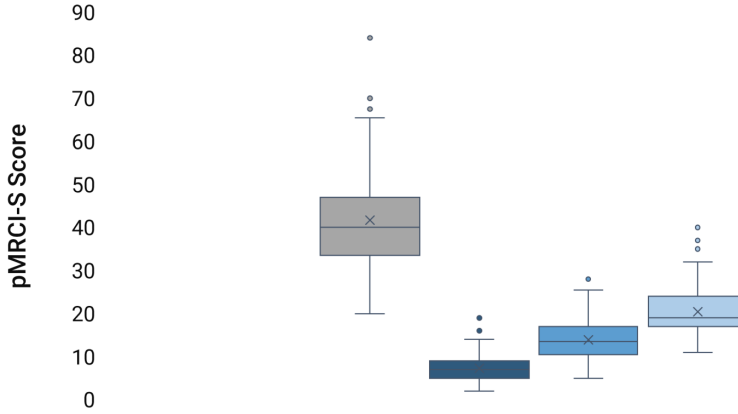


	TOTAL	1. IS	2. Other HTx	3. Comorbidities
pMRCI-S	42±11	18±3 (42%)	5±2 (13%)	19±11 (45%)
Medication count	12±3	3±0.4 (24%)	2±1 (17%)	7±3 (58%)

[a]The medication categories for this study were: 1-*Immunosuppressants*; 2-*Other treatments established in the post-HTx protocol*; and 3-*Drugs to treat comorbidities*. First, pMRCI-S scores and medication counts were significatively associated [*P*-value<.5]. Second, according to the influence of each medication category on the *total pMRCI-S score* 42 (SD11), *drugs to treat comorbidities* accounted for 19 (SD11) (45%), followed by *immunosuppression* 18 (SD3) (42%) and *other treatments per protocol* 5 (SD2) (13%). Third, high interpatient variability in therapeutic complexity was shown for *drugs to treat comorbidities* not observed for *immunosuppression* category.

Abbreviations: pMRCI-S, patient Medication Regimen Complexity Index Spanish version; r, Pearson's correlation coefficient; *P*, *P*-value; ±, standard deviation.

Figure 24: Impact of the pMRCI-S subsection scores on the *total pMRCI-S score*[a].



	TOTAL	Section A Dosage form	Section B Dosing frequency	Section C Additional instructions
pMRCI-S	42±11	7±4 (18%)	14±4 (33%)	21±6 (49%)

[a]Additional instructions are recommendations given to patients about taking their medication (e.g. to be taken on an empty stomach).

Abbreviations: ±, standard deviation. pMRCI-S, patient Medication Regimen Complexity Index Spanish version.

6.1.4. ASSOCIATION BETWEEN PMRCI-S AND OTHER VARIABLES

Factors predicting higher *total pMRCI-S score* in univariable linear regression analyses are shown in Table 10. Multivariate analysis showed that a higher count of (1) *drugs to treat comorbidities*, and (2) *other drugs per protocol* predicted a higher *total pMRCI-S score*. This association was not observed with *immunosuppressive treatment count* (Figure 25).

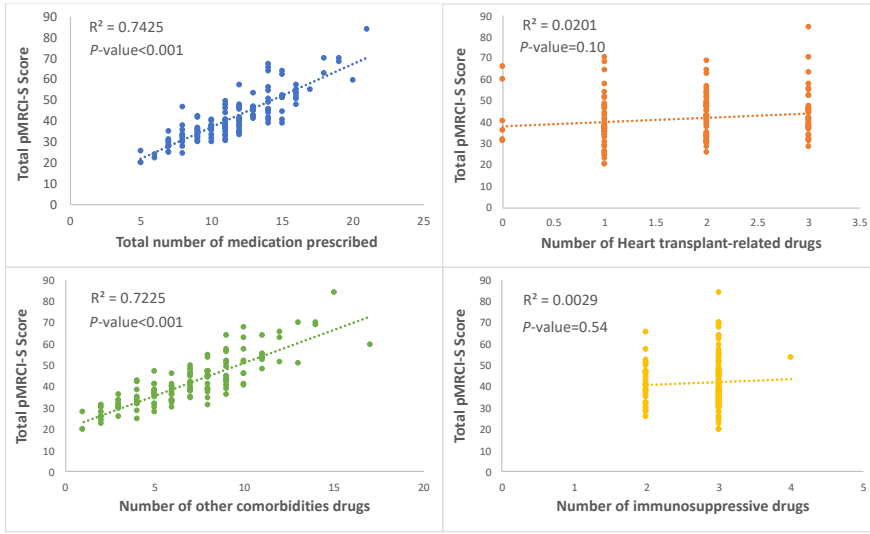
Table 10: Factors that resulted from univariable linear regression analyses and the multivariable analysis predicting *total pMRCI-S score*.

	Univariable analysis†		Multivariable analysis†	
Factor	Coefficients (95% CI)	*P*-value	Coefficients (95% CI)	*P*-value
Gender	-2.4 (-6.6-1.7)	.25	—	—
Age at the time of the study	0.3 (0.2-0.4)	**<.001**	—	—
Age at the time of HTx	0.2 (0.1-0.3)	**.002**	—	—
Total medication count	3.0 (2.7-3.3)	**<.001**	—	—
Immunosuppressants count	1.4 (-3.0-5.8)	.54	—	—
Other drugs per protocol count	1.9 (-0.4-4.1)	.10	2.2 (1.1-3.4)	**.001**
Drugs to treat comorbidities count	3.1 (2.8-3.4)	**<.001**	3.1 (2.8-3.4)	**<.001**
Patients without formal education	-9.2 (-14.9-(-3.4))	**.002**	—	—
Patients with disability	5.0 (1.2-8.8)	**.01**	—	—
Number of medical clinicians involved in patient follow-up	2.3 (1.3-3.3)	**<.001**	—	—
Number of comorbidities post-HTx	1.6 (0.9-2.3)	**<.001**	—	—
Need or requirement for caregiver	7.8 (3.3-12.4)	**.001**	—	—
Number of medication adverse effects	0.3 (-0.1-0.6)	.16	—	—
Patient's lack of awareness of consequences of non-taking IS	3.9 (0.03-7.8)	**.048**	—	—
Patient's perception of taking excessive medication	4.0 (0.1-7.8)	**.04**	—	—

† To identify multiple correlates of pMRCI-S, we first predicted association via univariable linear regression models. Variables whose odds ratios (ORs) suggested associations (i.e. confidence intervals not including 1.00) and other clinically relevant variables (gender, side effects and the drug count categories) underwent multiple linear regression analysis. The adjusted square coefficient of the model was 0.75.

Abbreviations: HTx, heart transplant; 95%CI, Confidence interval 95%; IS, immunosuppressive treatment; pMRCI-S, patient Medication Regimen Complexity Index Spanish version.

Figure 25: Impact of drugs count in each medication category on the *total pMRCI-S score*.



	TOTAL	1. IS	2. Other HTx	3. Comorbidities
Medication count	12±3	3±0.4 (24%)	2±1 (17%)	7±3 (58%)

The treatment categories were: 1-*Immunosuppressants*, 2-*Other treatments established in the post-HTx protocol*, 3-*Drugs to treat comorbidities*. The mean *total pMRCI-S score* was 42 (SD11, range 20-84). A higher *drug to treat comorbidities* count was associated with a higher *total pMRCI-S score* [*P*-value<.001]. The *immunosuppression count* or *other treatments per protocol count* were not associated with *total pMRCI-S score* [*P*-value>.05].

Abbreviations: pMRCI-S, patient Medication Regimen Complexity Index Spanish version; R^2, R-squared coefficient of determination; ±, standard deviation.

The impact of the *total pMRCI-S score* on clinical variables resulting from univariable logistic regression analyses and the final multivariate model is shown in Table 11. A higher *total pMRCI-S score* was predictive of (1) a higher number of solid malignancies; and (2) lower creatinine clearance. Our sensitivity analyses supported all the relationships observed.

Table 11: Clinical variables that resulted from univariable logistic regression analyses associated with higher pMRCI-S scores and the final multivariable analysis using an inverse probability-weighted model.

	Univariable analysis†		Multivariable analysis‡	
Clinical event	Coefficients (CI95%)	*P*-value	Coefficients (CI95%)	*P*-value
CAV				
Total pMRCI-S score	OR=1.00 (0.97-1.03)	.8	–	–
LVEF				
Total pMRCI-S score	R=-0.00 (-0.14-0.13)	.96	–	–
Total malignancies†				
Total pMRCI-S score	OR=1.06 (1.01-1.11)	.009	1.00 (0.95-1.06)	.88
1. IS pMRCI-S score	OR=1.01 (0.83-1.22)	.95	–	–
2. Per protocol pMRCI-S score	OR=0.97 (0.79-1.2)	.80	–	–
3. Comorbidities pMRCI-S score	OR=1.07 (1.02-1.12)	.007	–	–
Skin malignancies				
Total pMRCI-S score	OR=1.01 (0.96-1.06)	.71	–	–
Solid organ malignancies†				
Total pMRCI-S score	OR=1.07 (1.01-1.13)	.02	1.1 (1.02-1.18)	.02
1. IS pMRCI-S score	OR=1.08 (0.82-1.44)	.58	–	–
2. Per protocol pMRCI-S score	OR=0.88 (0.66-1.18)	.40	–	–
3. Comorbidities pMRCI-S score	OR=1.08 (1.02-1.14)	.01	–	–

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Renal function¥†				
Total pMRCI-S score	R=-0.86 (-1.19-(-0.53))	<.001	-0.81 (-1.21-(-0.42))	<.001
1. IS pMRCI-S score	R=1.51 (-0.12-3.14)	.07	—	—
2. Per protocol pMRCI-S score	R=1.06 (-0.68-2.80)	.23	—	—
3. Comorbidities pMRCI-S score	R=-1.07 (-1.40-(-0.74))	<.001	—	—

† Univariable analysis was performed by logistic regression to assess the association between events and the *total pMRCI-S score*. In events significantly correlated [*P*-value<.05] with the *total pMRCI-S score*, we also measured the association between the event and the *medication categories pMRCI-S scores*. Medication categories were 1-*Immunosuppressants*; 2-*Other treatments established in the post-HTx protocol*; and 3-*Drugs to treat comorbidities*.

‡ *Total pMRCI-S score* association with the event and corrected for confounding by using inverse probability weighting. The model to estimate inverse probability weights contains 12 variables detailed in statistical analysis.

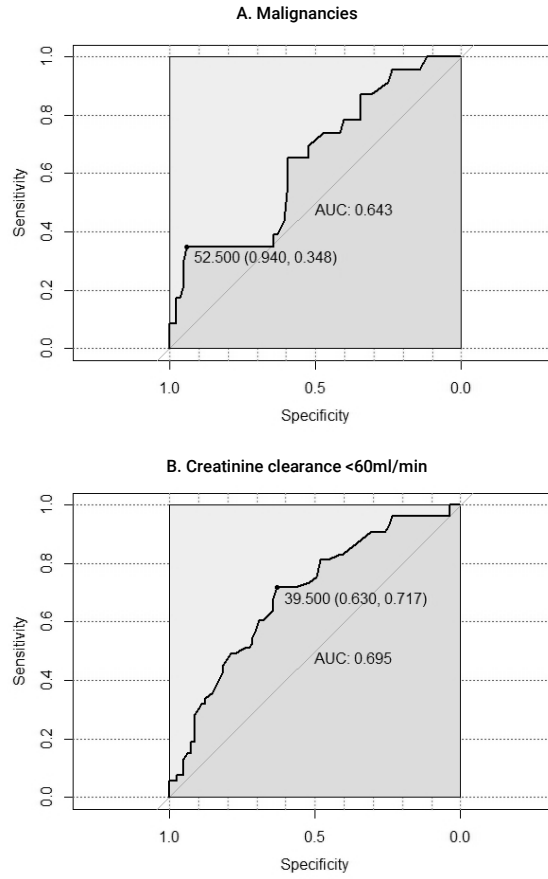
¥ Renal function measured as creatinine clearance (Cockcroft-Gault formula) ml/min.

Abbreviations: CAV, cardiac allograft vasculopathy; CI, confidence interval; LVEF, left ventricular ejection fraction; OR, odds ratio; pMRCI-S, patient Medication Regimen Complexity Index Spanish version; R, correlation coefficient r.

Regarding medication categories, only the *pMRCI-S score for drugs to treat comorbidities* showed a correlation with the same clinical, sociodemographic and therapeutical variables such as those observed for the *total pMRCI-S score* [*P*-value<.01].

As shown in Figure 26, a *total pMRCI-S* cut-off value of 53 best discriminated the risk of malignancies [AUC-ROC 0.64, sensibility 35%, specificity 94%)] Moreover, a threshold *total pMRCI-S score* of 40 was predictive of creatinine clearance <60 ml/min (AUC-ROC 0.70, sensibility 72%, specificity 63%).

Figure 26: The pMRCI-S value best discriminating malignancies and renal function according to the AUC-ROC analysis (Youden's method).



(A) The *total pMRCI-S* cut-off value best discriminating the risk of malignancies was 53 [OR=8.43, CI95% 2.42-29.30, *P*-value<.001]. The AUC-ROC was 0.64; sensitivity 35% and specificity 94%.

(B) The *total p-MRCI-S* threshold predictive of creatinine clearance <60 ml/min was 40 [OR=4.31, CI95% 2.04-9.11, *P*-value<.001]. The AUC-ROC was 0.70; sensitivity 72% and specificity 63%.

6.1.5. PATIENT-REPORTED OUTCOMES

Analysis of patients' medication beliefs showed that a total of 26% of the HTx recipients were unaware of the consequences of abandoning completely immunosuppression therapy (Table 12). Moreover, 61% of the patients believed they were taking excessive medication. Medication-related inconvenience was related to a higher total p-MRCI-S score [43 (SD12) versus 39 (SD10), *P*-value=.02] and decreased with recipient age [r=-18, *P*-value=.04].

The mean number of adverse effects reported by patients was 9 (SD5) with a quarter of them reporting 11 or more. The most prevalent were tremor (58%) followed by rash, acne and other skin disorders (53%) (Table 12). A higher total medication count [r=0.26, *P*-value=.003] and drugs to treat comorbidities count [r=0.26, *P*-value=.002] were significantly related to a higher prevalence of adverse effects.

Table 12: Patient-reported outcomes of the HTx recipients included in the study.

Variables	N=135
Patient-reported adverse effects, mean±SD (range) Q1:Q2:Q3	9±5 (0-25) 5;8;11
Type of side effect reported by patients, n(%)	
▪ Tremor	78 (58)
▪ Skin disorders	71 (53)
▪ Emotional disorders	64 (47)
▪ Muscular pain	64 (47)
▪ Cramps	64 (47)
▪ Visual impairment	60 (44)
▪ Weariness, tiredness, or fatigue	59 (44)
▪ Cephalea	53 (39)
▪ Insomnia	43 (32)
▪ Increased hair growth	39 (29)
▪ Diarrhea	34 (25)
▪ Dizziness	32 (24)
▪ Gingival disorder	27 (20)
Degree of patient-perceived inconvenience related to taking medication as prescribed every day (scale 0-10)	2±3 (0-9) 0;2;4
▪ mean±SD (range) Q1:Q2:Q3	74 (55); 49 (36);
▪ 0-2, 3-6, >7, n(%)	12 (9)
Patient perception of taking excessive medication, n(%)	79 (61)
Patient awareness of the importance of immunosuppressive therapy:	
1. If you discontinued taking your immunosuppressants completely, what do you think would happen to you?, n(%)	
▪ Nothing	3 (2)
▪ I don't know	34 (26)
▪ A different answer involving rejection	94 (72)
2. If you sometimes forgot to take your immunosuppressants, what do you think would happen to you?, n(%)	
▪ Nothing	12 (9)
▪ I don't know	41 (32)
▪ A different answer involving rejection	77 (59)

Abbreviations: HTx, heart transplant; Q1:Q2:Q3, lower, middle and upper quartiles; SD, standard deviation.

6.2. STUDY 2. INTERDISCIPLINARY MOBILE HEALTH MODEL TO IMPROVE THERAPY MANAGEMENT AND CLINICAL CARE AFTER HEART TRANSPLANTATION: AN IMPLEMENTATION STRATEGY STUDY

6.2.1. STAGE 1. DESIGN

Regarding patient access to technology and willingness to use mHealth services, of the 158 recipients >1.5 years from HTx, 142 (90%) patients were assessed for eligibility and 135 (85%) were finally recruited and analyzed. Of the patients excluded, 5 were follow-up in another transplant center, 5 had cognitive impairment and 6 were palliative. Of the 7 recipients who declined to participate, the reasons were lack of interest (n=2), lack of time to complete the interview (n=4) and feeling unwell to complete the interview (n=1).

Basic demographic and clinical data of the 135 chronic-stage HTx recipients interviewed are provided in Table 13. Briefly, the recipient's mean age was 57 (SD14) years; 31% were women. The mean time since transplant was 12 (SD7, range 2-31) years and was ≥15 years in 32%. The mean total number of drugs prescribed was 12 (SD3, range 5-21) to treat 6 (SD3, range 0-11) comorbidities post-transplant. Respondents' access to technology and willingness to use mHealth services are described in Table 13.

Patients' opinions led to the inclusion of the following elements: the figure of the tutor (a caregiver or a close family member), a proactive technical support service, and a website-profile for patients to complement the initial mHealth system.

Table 13: Chronic HTx recipients' (>1.5 years from transplant) sociodemographic and clinical characteristics, access to technology and willingness to use mHealth services.

Variables	N=135
Women, n(%)	41 (31)
Age at time of study inclusion, y ± SD	57±14
Time since transplant at the time of study inclusion ▪ Whole series, y ± SD ▪ >1.5-3; 3-5; 5-10; 10-15; ≥15, y ± SD	 12±7 (2-31) 11 (8); 16 (12); 27 (20); 37 (28); 43 (32)
Body mass index, kg/m2 ± SD	27±6
Heart failure etiology, n(%) ▪ Coronary/ischemic ▪ Cardiomyopathy ▪ Other	 36 (26) 58 (43) 41 (31)
Urgent HTx, n(%)	33 (24)
Educational attainment, n(%) ▪ No schooling ▪ Middle school graduate ▪ High school graduate ▪ University graduate	 15 (11) 58 (43) 25 (19) 36 (27)
Employment status, n(%) ▪ Disability ▪ Retired ▪ No previous employment ▪ Currently working	 74 (55) 20 (15) 7 (5) 33 (24)
Need or requirement for caregiver, n(%)	28 (21)
Lives with someone else, n(%)	115 (88)
Number of comorbidities, mean ± SD (range)	6±3 (0-11)
Patients with comorbidity post-transplant, n(%) ▪ High blood pressure ▪ Dyslipidemia ▪ Chronic kidney failure ▪ Osteopathies and chondroplasties ▪ Diseases of the nervous system ▪ Mood and anxiety disorders ▪ Digestive system diseases or disorders ▪ Diabetes mellitus ▪ Neoplasia ▪ Arthropathies	 94 (70) 73 (54) 58 (50) 52 (39) 51 (38) 49 (36) 42 (31) 42 (31) 39 (29) 27 (20)
Total number of drugs prescribed, mean ± SD (range) IQR	12±3 (5-21) 9;11;14

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Variables	N=135
Technology availability ▪ Number of devices per patient; mean ± standard deviation ▪ Types of devices owned by patients: mobile phone; computer; tablet; N(%)	 2±0.7 132 (98); 98 (73); 60 (45)
Internet access on patients' devices; N(%) ▪ 3G or 4G connection ▪ Only connects to the Internet using WIFI ▪ Does not know/no response	 112 (83) 18 (13) 5 (4)
Frequency of technology use; N(%) ▪ Often ▪ Sporadically ▪ Never	 87 (64) 35 (26) 13 (10)
Internet usage for health-related purposes; N(%) ▪ Often ▪ Sporadically ▪ Never	 41 (30) 43 (32) 51 (38)
mHealth approach initial assessment; N(%) ▪ Not very useful ▪ Useful ▪ Very useful ▪ Not yet known until the platform is tested	 2 (2) 92 (68) 40 (30) 1 (1)
mHeart® type of platform initial assessment; N(%) (multiple choice) ▪ Interested in using mHeart® mobile app ▪ Interested in using mHeart® website ▪ Not yet known until the platform is tested	 81 (60) 64 (47) 40 (30)
Initially requires a tutor to use the platform; N(%)	30 (22)

Abbreviations: N, number; SD, standard deviation; %, percentage; kg, kilograms.

According to stakeholder agreement about the benefits and barriers of an mHealth approach, of the 31 stakeholders invited to complete the survey, 2 nurses, 2 cardiologists and 1 social worker did not respond. No reasons were reported. Finally, 26 stakeholders responded the questionnaire, seventeen (65%) were women, with a mean age of 46 (SD10) years. The profiles of the 26 participants were: 6 (23%) physicians, 3 (11%) nurses, 5 (19%) pharmacists, 2 (8%) psychologists, 2 (8%) technology analysts, 3 (11%) key representatives of the local Health Authorities, 2 (8%) representatives of the regional Health Authorities, and 3 (12%) experts in mHealth.

The main gains of *the mHeart strategy* according to stakeholders' opinions are detailed in Table 14. Consensus was strong for the use of mHealth to improve therapy management (>85%). In this sense, the mHeart key features were mainly designed to the following aims presented in Textbox 10. A strong agreement (>75%) was also achieved for several other comprehensive benefits. Thus, the software features design was also directed to promote patient-provider interactions and communication, and to empower patients to play a more active role in their lifestyle, treatment, and self-care.

Textbox 10: ***The mHeart strategy*** **and software main aims according to stakeholders agreement.**

- Improve therapy management. (>85%)
  - Identify nonadherent patients and determinants of medication nonadherence.
  - Identify potential pharmacological interactions and adverse effects.
  - Improve patients' knowledge and management of regimens.
  - Reinforce patients' coresponsibility in their treatment.
  - To provide early medication adjustments and tailored interventions based on patient-reported outcomes.
- To promote patient-provider interactions and communication. (>75%)
- To empower patients to play a more active role in their lifestyle, treatment, and self-care. (>75%)

The major barriers of an mHealth approach identified by stakeholders are described in Table 14. Of note, agreement among stakeholders was weak for all items (<75%). Relevant barriers were prioritized to be overcome by the hospital's scientific advisory team due to their impact on implementation and scalability. First, ensuring the system's legal requirements, quality, and data security. Second, mitigating end users' digital divide (health providers and patients). Third, achieving system interoperability. Fourth, building the mHeart software in a global structure that may be easily adapted to other complex diseases.

Table 14: Stakeholders' agreement on the benefits and limitations of an mHealth approach in multimorbid patients with polypharmacy such as the HTx population.

Stakeholders' agreement (n=26 stakeholders)	N(%)
Benefits	
Improves patients' knowledge of therapy, management, and medication adherence	23 (88%)
Improves the continuity of care and the flow of information between health providers and levels of care	21 (81%)
Allows patients to be empowered and actively manage their disease and treatment	20 (77%)
Resolves patient and caregiver queries from home due to the 2-way health care provider-patient communication	20 (77%)
Monitoring and managing patient-reported outcomes such as symptoms and adverse effects to drugs	17 (65%)
Focuses on health promotion and prevention to reduce the number of acute events	17 (65%)
Increases the cost-effectiveness of resources by reducing both scheduled and urgent visits due to decompensation	17 (65%)
Facilitates innovation in health and documentation of evidence that translates into measurable health outcomes	17 (65%)
Reduces inequalities in access to the health system due to traveling difficulties or lack of resources	10 (38%)
Improves patients' experience because of close communication with health providers	4 (15%)
Limitations	
Increase in staff workload for staff	15 (58%)
Lack of institutional guidelines to set up and implement systems and accreditation of mobile health applications	14 (54%)
Risk of not sharing the patient's registered information with other levels of care or with other apps (used to manage other health conditions)	13 (50%)
Risk of not protecting confidential patient data	6 (23%)
Risk of creating inequalities in patient care due to resistance to use technology or the digital divide	6 (23%)
Lack of guarantee of the long-term economic sustainability of research projects for innovative technologies and companies that develop the systems	4 (15%)

6.2.2. STAGE 2. DEVELOPMENT

As a result of the Alpha testing focus groups, additional features and improvements in functionality were included. The list of improvements is fully detailed in Appendix 7. Beta testing feedback greatly improved usability, the suggestions not affecting usability or security were postposed to subsequent mHeart improvement phases. New developers may incorporate these challenges into their initial design of the system:

- Automatic responses to consultations regarding interactions with concomitant therapies connected to official database.
- Programming periodic changes to the mHeart questionnaire type or order of items (e.g. adherence or general condition). This will prevent the patient from responding in a routine manner and the system from losing sensitivity in identifying nonadherent patients.
- Set up a discussion forum for patients.
- Enable patients at home to print the medication chart and the calendar with all the tasks planned in the tool's agenda by health providers and patients.
- Connecting the mHeart Agenda with the Hospital Visit Scheduling System. To automatically download the appointment schedules on the mHeart system.
- To develop a decision support system based on artificial intelligence algorithms (patterns and prediction rules).
- Translating the platform into other languages to make the tool usable in other countries.

Important contributions were also obtained from patient associations opinions. First, participants showed interest in using mHealth to manage their chronic comorbidities. Moreover, they highlighted their interest in 2-way

messaging with the clinical team. Participants also compared the tool with other free downloadable tools from online stores. Thus, the main additional value of mHeart noticed by them was primarily that it was adapted to their condition by transplant providers and, secondly, that they obtain clinical feedback on the activity recorded. Finally, they requested a patients' chat room and a patient-provider teleconference module.

The entire technical development and user testing processes resulted on the mHeart final prototype primarily directed to carry out integral therapy management and clinical care in transplant populations and specifically in HTx recipients. (Appendix 1 and 6) The system is a mobile phone app connected to a website (215) for use by health providers and patients. The app can be downloaded free from the online Google (195) and Apple (196) stores. The general layout is represented in Figure 20 and is detailed in the online Mendeley dataset. (1) From a clinical point of view, the tool can be simultaneously used on distinct devices to facilitate support from caregivers or tutors. The use of the platform by patients and the multidisciplinary team is summarized in Appendix 6. The behavioral framework and theory-based interventions that could be delivered using the mHeart tool in future intervention studies are listed in Appendix 2. More details about functionalities and a video of the clinical use of the mHeart mobile application are also provided in the online Mendeley dataset. (1)

6.2.3. STAGE 3. INTEROPERABILITY AND IMPLEMENTATION

Diverse solutions to address implementation were settled by the scientific advisory team. First, mHeart was set up to be compatible with different systems and applications to ensure that users employ their own phones, computers, or tablets. Second, technical support was outsourced (by the technological development firm) to provide initial training on mHeart skills to patients and health providers as well as to solve queries. Finally, institutional protocols were created to standardize the new clinical workflows.

Additionally, based on participants' expertise [n=2, (100%)], the pathways to overcome the lack of integration and communication between mHeart and electronic health records were separated into local and institutional solutions. Regarding local solutions, the strategies embedded allowed 2-way data exchange between mHeart and the hospital information system. First the mHeart system requests sociodemographic patient data from the hospital information system. Data can refer to a new patient or an update on the patient's data. This is via a synchronous high level-7 message patient query through the Simple Object Access Protocol. Second, once a week, a data report containing all the mHeart patient-reported outcome measures is uploaded to the hospital information system. This is via an implicit File Transfer Protocol over the Transport Layer Security server. A security process identifies the report and assigns it to the patient in the hospital information system. Only the latest report can be consulted as a clinical document. More details are also provided in the online Mendeley dataset. (1)

According to institutional solutions identified, first, the patient's data report could be also integrated with the regional electronic clinical record. With this report, any provider in the catchment area can monitor patients from any care level (e.g., primary care, hospital care). Second, in 2017, the Regional Health care System approved mHeart® to be integrated with La Meva Salut, which is a patient health website allowing citizens to interact with the regional health care system.

6.2.4. STAGE 4. QUALITY, SECURITY AND LEGAL REQUIREMENTS

Based on expert feedback, workable solutions were identified and listed in Table 15 to ensure legal, security, and data protection, medical technology intellectual property, medical device regulations, and quality evaluation. The solutions embedded, could be used by other developers as a checklist to ensure minimum standards but are not limited to these solutions.

Table 15: Workable solutions to ensure the quality and security of the eHealth platform.

Processing personal data with confidentiality and security
▪ Comply with the national regulations on high level confidential personal data. ▪ Obtain support from the hospital's Department of Data Confidentiality and Data Analysis. ▪ Ensure the quality of the Data Center through certification. ▪ Use secure connections for data integration between systems. ▪ Perform an annual audit of confidentiality and security by an external firm. ▪ Ensure users' duties: (i) patients should sign a non-disclosure agreement; (ii) passwords require updating every 6 months; (iii) acceptance of the mHeart's conditions of use are a pre-requisite and should be always available for future consultation by users.
Intellectual and industrial property recommendations
▪ Obtain support from experts on medical technology intellectual and industrial property. ▪ Sign a collaboration contract between the hospital and the developers' private firm. ▪ Register the platform trademark (i.e. mHeart®). ▪ Register the platform content on intellectual property registers.
Medical device certificate
▪ Adopt the legislation requirements on medical device regulations. (182,216) CE marking as a class IIa medical device was obtained for mHeart
Certification granted by a local Institution
▪ Certificate of app quality by local institutions. AppSaludable (217) is already adopted for mHeart. AppSalut (218) is in the process of adoption by Fundació TicSalut (Regional Health Department). Some other options are: British (219,220), iSYS Score (221), and uMARS (222,223).
Content quality
▪ Obtain institutional endorsement by scientific societies related to the population field. Written support for mHeart was provided by: ▫ The regional transplant organization (OCATT) (October 31, 2016). ▫ The regional transplant society (SCT) (October 10, 2017). ▫ La Meva Salut homologation approval by the regional Health Government (October 20, 2016). ▪ Obtain written endorsement from patient associations and support groups. Written support for mHeart was provided by: ▫ "Club de la Cremallera", Clinic Hospital (November 3, 2016). ▫ "Cors Nous", Bellvitge Hospital (November 3, 2016).

6.3. STUDY 3. THE MHEART MOBILE APP TO DETECT MEDICATION NONADHERENCE IN THE HEART TRANSPLANT POPULATION: VALIDATION STUDY

6.3.1. PARTICIPANT CHARACTERISTICS

A total of 31 acute-stage HTx recipients were included and analyzed, and no attrition was observed (Figure 18). The mean follow-up was 2.3 (SD0.9) months. The mean age was 54 (SD12) years and 22 (71%) participants were men. The mean time between HTx and the study was 1.2 (SD0.8) years. The patients' demographic and clinical characteristics are detailed in Table 16. At baseline, 22 (71%) patients used technologies frequently. Most of the patients [n=22 (71%)] reported that mHeart could be "*useful*" or "*very useful*" [n=4 (13%)]. A third of the patients [n=9 (29%)] reported they needed personal assistance to get started using the mHeart platform.

Table 16: Demographic and clinical characteristics of the early-stage HTx recipients included.

Variables	N=31
Recipient gender (women), n(%)	9 (29)
Recipient age at the time of the study, years ± SD	54 ± 12
Donor age, years ± SD	49 ± 12
Donor sex (men), n(%)	13 (42)
Time from HTx transplant, years ± SD	1.2 ± 0.8
Body mass index, kg/m2 ± SD	25 ± 54
Cytomegalovirus mismatch (recipient-/donor+), n(%)	5 (16)
Heart failure etiology, n(%) ▪ Congenital ▪ Coronary/ischemic ▪ Myocarditis ▪ Cardiomyopathy ▪ Hypertrophic cardiomyopathy ▪ Other	 4 (13) 12 (39) 1 (3.2) 12 (39) 1 (3) 1 (3)
Urgent HTx, n(%)	15 (48)
Total ischemia time, min±SD	198 ± 48
Number of recipients with at least 1 episode of ARE, median (Q1-Q3)	4 (13)
AMR, n(%)	1 (5)
CAV, n(%)	9 (29)
LVEF, %±SD	66 ± 8
Educational attainment, n(%) ▪ No schooling ▪ Middle school graduate ▪ High school graduate ▪ University graduate	 5 (16) 13 (42) 7 (23) 6 (19)
Employment status, n(%) ▪ Temporary medical leave ▪ Long-term Disability ▪ Retired ▪ No previous employment ▪ Currently employed	 8 (26) 12 (39) 7 (23) 2 (7) 2 (7)
Need or requirement for caregiver, n(%)	11 (36)

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Variables	N=31
Lives with someone else, n(%)	28 (90)
Number of comorbidities ▪ Pre-transplant, mean±SD (range) ▪ Post-transplant, mean±SD (range)	 3.4 ± 2.5 2.8 ± 2.3
Medical clinicians (other than the transplant team), mean±SD (range)	2.4 ± 0.8
Number of patients who were always visited by the same primary care physician, n(%)	28 (90)
Number of primary care visits in the last month, n(%) ▪ None ▪ 1-2 visits ▪ >3 visits	 20 (65) 11 (36) None
Reasons for primary care visits, n(%) ▪ Medical consultation ▪ Refill prescriptions ▪ Other	 8 (26) 20 (65) 3 (10)
mHeart initial patient assessment; n(%) ▪ Not very useful ▪ Useful ▪ Very useful ▪ Not yet known until the platform is tested	 4 (13) 22 (71) 4 (13) 1 (3)
Frequency of technology use; n(%) ▪ Frequently ▪ Occasionally ▪ Never	 22 (71) 6 (19) 3 (10)
Use of health-related technology	22 (71)
Patient assistance in using the platform, n(%) ▪ Yes ▪ No ▪ Not yet known until the platform is tested	 9 (29) 22 (71) 0 (0)

Abbreviations: AMR, antibody-mediated rejection; ARE, acute cellular rejection episode; BMI, body mass index; CAV, cardiac allograft vasculopathy; HTx, heart transplantation; LVEF, left ventricular ejection fraction; SD, standard deviation.

6.3.2. POLYPHARMACY AND DETERMINANTS OF MNA

Polypharmacy was common; the mean total medication count was 13 (SD4, range 7-18), exceeding 14 drugs/day in 11 (36%) patients. Patients reported an average of 6 (SD4) adverse effects. As many as 19 (61%) of them reported being self-reliant for medication management.

Medication-related inconvenience was moderate to high (>6 of 10) in 8 (25%) patients. As many as 23 (74%) of them believed they were taking excessive medication. The danger of sometimes not taking immunosuppressive drugs was understood by 13 (42%) recipients. Furthermore, 10 (32%) recipients were unaware of the consequences of completely abandoning antirejection therapy. More details are provided in Table 17.

Table 17: Patients' therapeutic characteristics and treatment-related patient-reported outcomes (PRO).

Variables	N=31
Patient autonomous for preparing and taking medication, n(%)	19 (61)
Reasons for lack of autonomy in medication intake, n(%)	
▪ Reports neurological symptoms limiting ability (e.g., confusion, lack of memory)	4 (33)
▪ Reports fear of forgetting unless given help	1 (8)
▪ Reports receiving a lot of information after transplantation	3 (25)
▪ Does not know the reason	4 (33)
Knowledge of the therapeutic regimen	
▪ Names of the drugs remembered	
▫ Mean (range)	6 (0-16)
▫ Proportion of drugs remembered the total prescribed, %	54
▪ Doses of the drugs remembered	
▫ Mean (range)	2 (0-7)
▫ Proportion of drugs remembered the total prescribed, %	25
▪ Intake of the drugs remembered	
▫ Mean (range)	6 (0-13)
▫ Proportion of drugs remembered the total prescribed, %	59
▪ Indications of the drugs remembered	
▫ Mean (range)	5 (0-13)
▫ Proportion of drugs remembered the total prescribed, %	43

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Variables	N=31
Degree of inconvenience perceived by patients related to taking their medication as prescribed every day (scale 0-10), mean ± SD (P 25, 50, 75, 90)	4 ± 3 (2, 3, 6, 7)
Patients' perception of taking excessive medication, n(%)	23 (74)
Patients' awareness of the importance of immunosuppressive therapy, n(%)	
1. If you discontinued taking your immunosuppressants completely, what do you think would happen to you?	
▫ Nothing	1 (3)
▫ I don't know	10 (32)
▫ A different answer involving rejection	20 (65)
2. If you sometimes forgot to take your immunosuppressants, what do you think would happen to you?	
▫ Nothing	1 (3)
▫ I don't know	13 (42)
▫ A different answer involving rejection	17 (55)
3. Did you modify the immunosuppressant timetable in the last week?	
▫ No	23 (74)
▫ >once	8 (26)
▫ I don't remember	0 (0)
4. Did you modify the immunosuppressant timetable since the last visit?	
▫ No	21 (68)
▫ >once	5 (16)
▫ >5 times	5 (16)
▫ I don't remember	0 (0)
Patient's reported adverse effects, mean ± SD (range)	6 ± 4 (0-11)
▪ ≥2 adverse effects	25 (81)
▪ ≥5 adverse effects	19 (61)
Type of adverse effect reported by patients, n(%)	
▪ Visual impairment	43 (25)
▪ Psychological (emotional disorders, insomnia)	42 (24)
▪ Neurological (tremor, dizziness, headache)	39 (22)
▪ Mucosa and aesthetic (thrush, gingival disorder alopecia, increased hair growth, other skin disorders and visual disorders)	22 (13)
▪ Pain (muscular pain, joint pain)	15 (9)
▪ Gastric (diarrhea, nausea, constipation, vomiting, etc.)	12 (7)
▪ Muscular (weariness, tiredness or fatigue, cramps)	2 (1)

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Variables	N=31
Medication categories, n(%)	
▪ Immunosuppressants, mean ± SD (range)	3±0.4 (2-4)
▫ mycophenolate mofetil (MMF)	22 (71)
▫ mycophenolate sodium (MPS)	6 (19)
▫ azathioprine	0
▫ cyclosporine	1 (3)
▫ tacrolimus extended release	14 (45)
▫ tacrolimus immediate release	16 (52)
▫ sirolimus	0
▫ everolimus	2 (6)
▫ prednisone	30 (97)
▪ Other treatments established in HTx protocol	
▫ calcium + vitamin D	29 (94)
▫ Aspirin	23 (74)
▫ pravastatin	26 (84)
▫ valganciclovir	16 (52)
▫ cotrimoxazole + folinate acid	18 (58)
▫ antacid (IBP or antiH2)	30 (97)
▪ Other drugs to treat comorbidities >20% (ATC code)	
▫ Group A. Alimentary tract and metabolism	25 (20)
▫ Group C. Cardiovascular system	23 (19)
▫ Group G. Genitourinary system and sex hormones	17 (14)
▫ Group N. Nervous system	32 (26)
▪ Over-the-counter drugs, mean ± SD (range)	2 ± 1
Total number of drugs prescribed, mean ± SD (range)	13 ± 4 (7-18)
Patients with polypharmacy, n(%)	
▪ ≥5 drugs; ≥8 drugs; ≥14 drugs	31 (100); 27 (87); 11 (34)

Abbreviations: HTx, heart transplant; SD, standard deviation.

6.3.3. VALIDITY MEASURES

Content validity

Regarding the adequate representability and relevance of the ePROMs to be included in the mHeart system, the Haynes-Sackett and the Morisky-Green-Levine questionnaires showed excellent agreement (>85%) while the SMAQ questionnaire showed poor agreement (<75%) (Table 18).

Table 18: Expert panel inter-rater agreement on the most suitable questionnaires to measure medication adherence using the mHeart platform, measured by the Group Consensus Method.

Round	Adherence ePROM	Agreement[a]	*P*-value[b]	Inclusion on mHeart
Round 1	Haynes-Sackett	13 (93%)	.11	—
	Morisky-Green-Levine	12 (86%)	.27	—
	SMAQ	10 (71%)	.50	—
Round 2	Haynes-Sackett	14 (100%)	.03	Included
	Morisky-Green-Levine	13 (93%)	.11	Included
	SMAQ	6 (43%)	.99	Non-included

[a] Percentages of agreement. An agreement >75% of the expert panel was considered adequate.

[b] *P*-value was one-sided to test if P was greater than .75 (75%).

Abbreviations: ePROMs, electronic patient-reported outcome measure to assess medication adherence; SMAQ, Simplified Medication Adherence Questionnaire validated in Spanish transplant population.

The suitability of the medication difficulties to support its addition to the Haynes-Sackett electronic version was excellent (>80%). Item agreement is detailed in Table 19.

Table 19: Expert panel inter-rater agreement on several criteria for the 6 reasons for MNA Haynes-Sackett ePROM, measured by the Nominal Group Consensus method.

Reasons for MNA Haynes-Sackett ePROM	Intuitive[a]	Easy[a]	Brief[a]	Useful[a]	Overall agreement[b] (*P*-value[c])
"I sometimes forget to take my medication"	14 (100%)	14 (100%)	14 (100%)	14 (100%)	100% (<.001)
"I lack information on medication and/or the disease"	14 (100%)	13 (93%)	14 (100%)	14 (100%)	98% (<.001)
"I feel demotivated about taking my medication"	12 (86%)	11 (79%)	14 (100%)	13 (93%)	89% (.01)
"Because of side effects or fear of having them"	13 (93%)	13 (93%)	14 (100%)	13 (93%)	95% (<.001)
"Because of complex regimens and/or inconvenient regimens"	13 (93%)	8 (57%)	14 (100%)	14 (100%)	88% (.02)
"Because of other reasons"	12 (86%)	14 (100%)	13 (93%)	12 (86%)	91% (.004)

[a] Item criteria full description: true to the original in-clinic test; useful to evaluate medication adherence construct; intuitive; brief or fast to complete; easy-to-understand language.

[b] Percentages of agreement. An agreement >75% of the expert panel was considered adequate.

[c] *P*-value was one-sided to test if P is greater than .75–75%.

Abbreviations: ePROMs, electronic patient-reported outcome measures to assess medication adherence; MNA, medication nonadherence.

The overall agreement between the ePROMs and the on-site PROMs was strong for the Haynes-Sackett (*Kappa*=0.826, P<.001) and for the Morisky-Green-Levine (*Kappa*=1, P<.001) questionnaires. Item agreement is detailed in Table 20.

Table 20: Expert panel agreement on item characteristics of ePROMs compared with on-site PROMs, measured by the Nominal Group Consensus method.

PROM item Kappa (*P*-value)	True[a]	Useful[a]	Intuitive[a]	Brief[a]	Easy[a]
Item 1 MGL	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)
Item 2 MGL	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)
Item 3 MGL	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)
Item 4 MGL	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)	1 (<.001)
Item 1 HS	1 (<.001)	0.6 (<.01)	0.4 (.04)	1 (<.001)	1 (<.001)

[a] Item characteristics full description: true to the original in-clinic test; useful to evaluate medication adherence construct; intuitive; brief or fast to complete; easy-to-understand language.

Abbreviations: HS, Haynes-Sackett questionnaire; MGL, Morisky-Green-Levine 4-item questionnaire; PROMs, patient-reported outcome measure to assess medication adherence.

Convergent and discriminant validity

The correlation between medication adherence domains of the PROMs compared with the SMAQ questionnaire are shown in Table 21.

Table 21: Convergent and discriminant validity assessed by the correlation of medication adherence PROMs with the SMAQ questionnaire.

Validity property	Medication adherence PROMs	Method	*Phi* (*P*-value)	Interpretation
Convergent	Morisky-Green-Levine vs SMAQ	Electronic	0.6 (<.001)	Strong correlation Measures similar Adh. domains
		In-clinic	0.9 (<.001)	
Divergent	Haynes-Sackett vs SMAQ	Electronic	0.3 (.12)	Weak correlation Measures different Adh. domains
		In-clinic	0.4 (.04)	

Abbreviations: HS, Haynes-Sackett questionnaire; MGL, Morisky-Green-Levine 4-item questionnaire; PROMs, patient-reported outcome measure to assess medication adherence. Adh., medication adherence; PROMs, patient-reported outcome measure to assess medication adherence; SMAQ, Simplified Medication Adherence Questionnaire validated in Spanish transplant population.

Reproducibility

The equivalent forms reliability method showed a very strong association between the scores obtained using the ePROMs and on-site PROMs [*Phi*>0.7, *P*<.001] (Table 22).

Table 22: Reliability of medication adherence ePROMs compared with on-site PROMs using the equivalent forms reliability method.

Medication adherence PROMs	*Phi* coefficient	*P*-value
HS Overall	0.8	<.001
MGL Overall	0.7	<.001
MGL Item 1	0.7	<.001
MGL Item 2	0.7	<.001
MGL Item 3	0.6	<.001
MGL Item 4	1	<.001

Abbreviations: ePROMs, electronic patient-reported outcome measure to assess medication adherence; HS, Haynes-Sackett questionnaire; MGL, Morisky-Green-Levine 4-item questionnaire; PROMs, patient-reported outcome measure to assess medication adherence.

For the test-retest reliability method, all participants remained stable between assessments. Low reproducibility was observed, while medication adherence improved during this interval according to both types of ePROM (Table 23).

Table 23: Test-retest reliability method to measure stability of medication adherence ePROM scores over time.

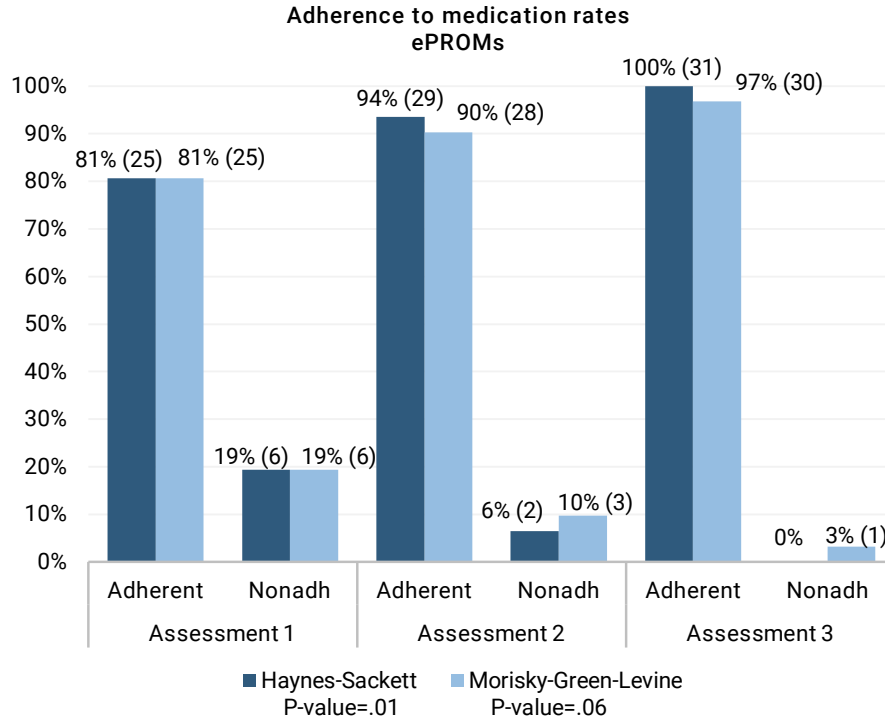
ePROMs	Assessment 2		Assessment 3		Kappa	*P*-value	Interpretation
	Adherent	Nonadh.	Adherent	Nonadh.			
HS	29 (94%)	2 (7%)	31 (100%)	0 (0%)	0.6	.002	Moderate stability
MGL	28 (90%)	3 (10%)	30 (97%)	1 (3%)	0.3	.11	Poor stability

Abbreviations: ePROMs, electronic patient-reported outcome measure to assess medication adherence; HS, Haynes-Sackett questionnaire; MGL, Morisky-Green-Levine 4-item questionnaire; Nonadh., medication nonadherence.

Responsiveness or sensitivity to change

According to the change in medication adherence over time, similar rates were obtained in assessment 2 between ePROMs and PROMs (Figure 27). Details for each item are provided in Table 24.

Figure 27: Medication adherence rates and improvement between study assessments.



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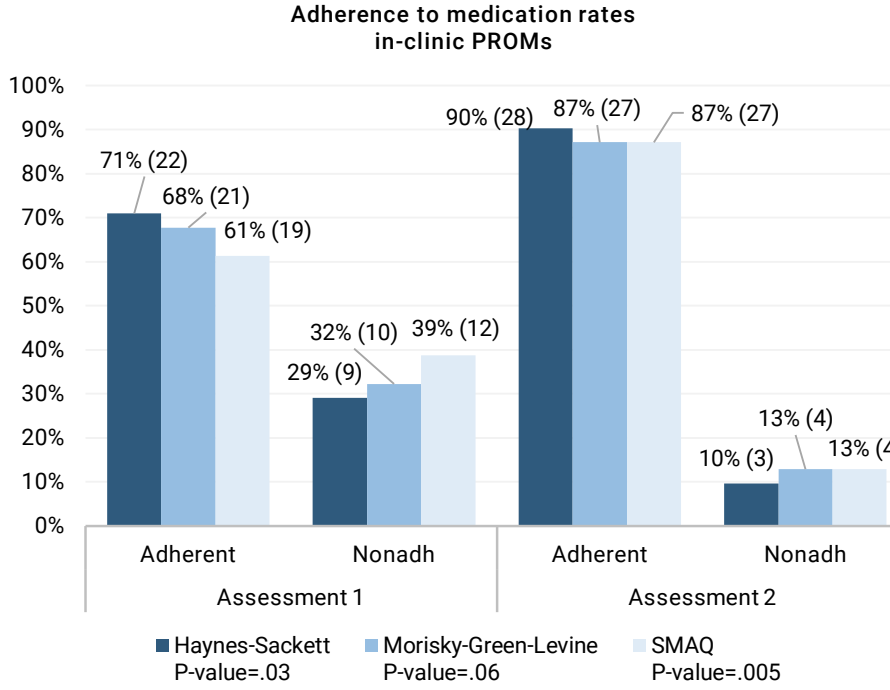

The behavioral-based intervention established by the pharmacist was performed between Assessments 1 and 2 (1 month at least). There was a 7-day gap between Assessments 2 and 3 to allow the reproducibility test re-test study without provider interactions. The Haynes-Sackett and Morisky-Green-Levine (4-item) questionnaire measures adherence to overall medication. The SMAQ questionnaire measures adherence to immunosuppression.

Abbreviations: PROMs, patient-reported outcome measure; Nonadh., Nonadherence to medication; SMAQ, Simplified Medication Adherence Questionnaire validated in the Spanish transplant population.

Table 24: Nonadherence rates in early-stage heart transplant patients listed by item in the study period.

Medication adherence measures[a] (N=31)	Assessment 1		Assessment 2		Assessment 3
	In-clinic	mHeart	In-clinic	mHeart	mHeart
Haynes-Sackett					
Overall score	**29%**	**19%**	**10%**	**7%**	**0%**
HS 1	NA	7%	NA	3%	0%
HS 2	NA	0%	NA	0%	0%
HS 3	NA	0%	NA	0%	0%
HS 4	NA	3%	NA	0%	0%
HS 5	NA	3%	NA	0%	0%
HS 6	NA	7%	NA	3%	0%
MGL					
Overall score	**32%**	**19%**	**13%**	**10%**	**3%**
MGL 1	26%	16%	3%	3%	0%
MGL 2	0%	3%	0%	0%	0%
MGL 3	7%	10%	4%	7%	0%
MGL 4	1%	3%	1%	0%	0%
SMAQ					
Overall score	**39%**	**NA**	**13%**	**NA**	**NA**
SMAQ 1	26%	NA	3%	NA	NA
SMAQ 2	0%	NA	0%	NA	NA
SMAQ 3	23%	NA	4%	NA	NA
SMAQ 4	3%	NA	0%	NA	NA
SMAQ 5					
▫ 1-2 days	**7%**	**NA**	**2%**	**NA**	**NA**
▫ >3 days	**3%**	**NA**	**0%**	**NA**	**NA**
SMAQ 6					
▫ 1 day	**19%**	**NA**	**7%**	**NA**	**NA**
▫ ≥2 days	**7%**	**NA**	**3%**	**NA**	**NA**

[a] Nonadherence to medications refers to the implementation phase, is defined as "actual dosing does not correspond to the prescribed dosing regimen due to delays, omissions or extra doses" and is measured by self-report questionnaires. Delays refer to irregularities with the intake schedule (±2 hours).

Abbreviations: ePROMs, electronic patient-reported measures; HS, Haynes-Sackett medication adherence questionnaire; MGL, Morisky-Green-Levine medication adherence questionnaire; NA, not applicable.

Interpretability

The ePROM scores showed a non-significant underestimation (*P*>.05) of MNA rates at assessment 1, but not at assessment 2. Almost all the patients were adherent according to the ePROMs at assessment 3. The baseline overall MNA rate in-clinic was 32% measured by Morisky-Green-Levine PROMs. According to SMAQ, 12 (39%) HTx recipients were nonadherent to immunosuppressive treatment. The theory-based multifaceted intervention program showed significant [*P*<.05] improvements in MNA, ranging from 16% to 26%, depending on the questionnaire used.

Burden

Regarding the criteria of respondent burden, 25 (81%) patients reported spending 1-2 minutes completing the ePROMs, while the average time for in-clinic PROMs was 6 minutes (SD2, range 3-9). All patients were able to learn the basic digital competencies needed to complete the ePROMs. No missing values were found using the 2 methods.

According to administrative burden, the total average time spent per day by the pharmacist on mHeart was 33 minutes (SD6, range 21-44). This time allowed follow-up of all the patients. The on-site PROMs required an office to be available and an average of 45 minutes for each individual assessment. Both methods required the professional to be trained in motivational interviewing, medication management, and transplant basics.

6.3.4. PATIENT SATISFACTION AND USABILITY SURVEY

The completion rate was 29/31 patients. The reasons for non-response to the survey are detailed in Figure 18. Patients reported no inconvenience due to the mHeart intervention approach employed. The ePROM appropriateness score was 8 (SD2) (scored 0-10). Overall satisfaction with the mHeart approach was 9 (SD2) (scored 0-10). All 29 patients (100%) would recommend the mHeart platform to other recipients. Regarding patient suggestions for improving the platform, 7 (24%) patients made 8 suggestions and 22 (76%) responded "*No, I like it just as it is*".

Improvements were implemented based on patient feedback, for instance:

- To avoid patient recall bias, the order of the ePROM items was designed to automatically change whenever the test is completed.
- Patients consult graphically any values they recorded in mHeart (e.g. blood pressure).
- Pop-up alerts were established to let patients know that a new text message from provider had arrived.
- Diverse actions were implemented to decrease telephone calls by patients to enquire about the compatibility of new therapies:
    - The usability of the mHeart function to enquire about new therapies was improved.
    - Text messages were sent to the patients explaining how to use this function.

Details of each survey item score, patient suggestions and the subsequent improvements are provided in Appendix 8.

6.4. STUDY 4. IMPROVING PATIENTS' EXPERIENCE AND MEDICATION ADHERENCE AFTER HEART TRANSPLANT USING A MULTILEVEL MHEALTH INTERVENTION: THE MHEART RANDOMIZED CLINICAL TRIAL

6.4.1. DEMOGRAPHIC AND CLINICAL INFORMATION

The Consolidated Standards of Reporting Trials (CONSORT) flow chart is shown in Figure 28. A total of 180 HTx recipients were analyzed; of these, 134 were chronic-stage [intervention group N=71; control group N=63] and 46 were acute-stage recipients. An attrition rate of 4% was observed. The mean follow-up was 1.6 (SD0.6) years.

The patients' demographic and clinical characteristics are summarized in Table 25. Mean age was 55 (SD14) years; 30% were women. The mean time from HTx was 8 (SD8) years and was ≥15 years in 24% of the recipients. Polypharmacy (≥8 drugs) was common (79%); the mean total medication count was 10 (SD3, range 3-19). Most of the patients were under triple immunosuppression treatment consisting of tacrolimus (79%), mycophenolate (79%) and prednisone (89%). The mean number of comorbidities was significantly higher post-HTx than pre-HTx [R=.316, *P*-value=.000]. Nearly half (54%) of the recipients visited only their primary care physician to refill prescriptions. As many as 24% of the patients needed a caregiver, and 21% were currently employed. According to lifestyle habits, in the last 3 months, 29% of the patients reported not practicing any sport, 8% having smoked, 62% reported alcohol consumption (30% >3 times/per week) and 3% reported drug consumption.

Figure 28: Patient flow chart.

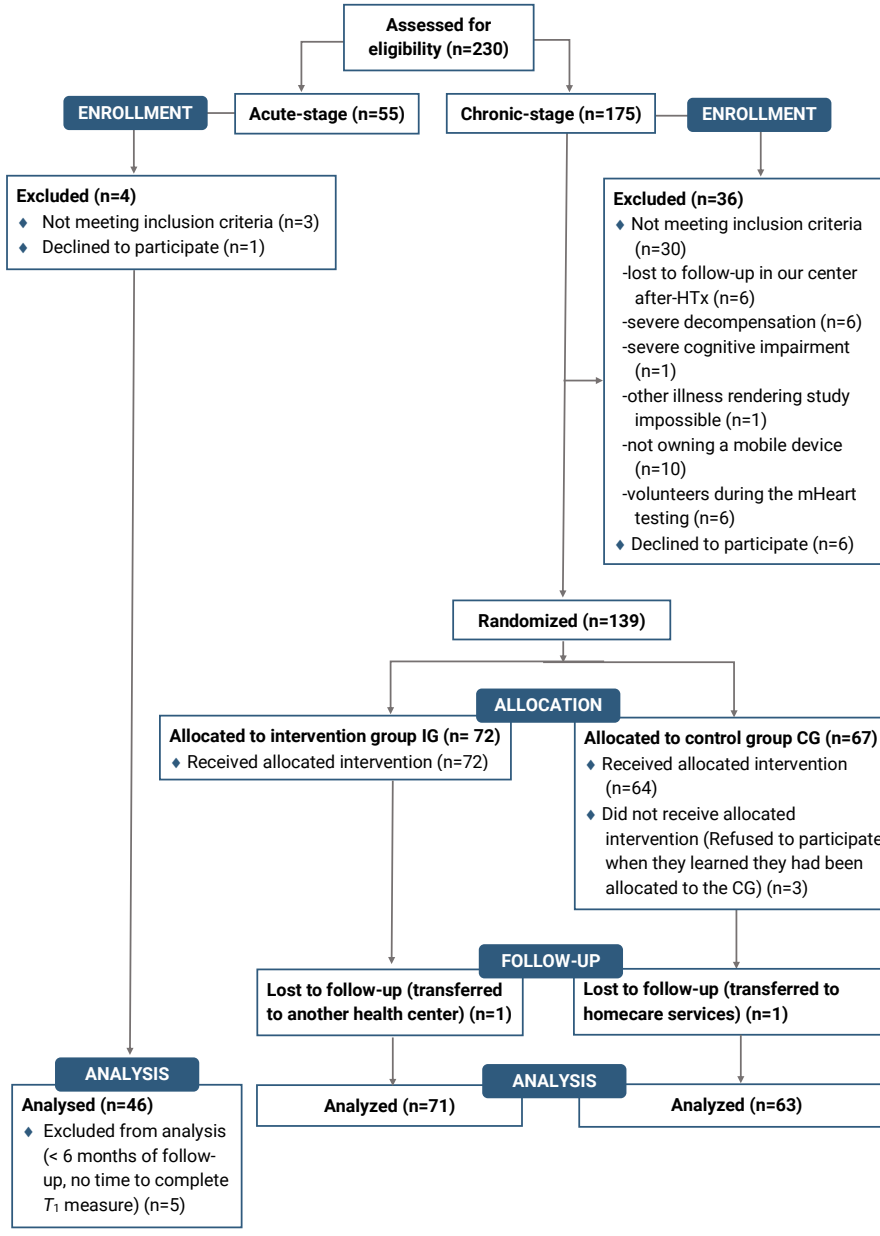

Table 25: Demographic and clinical information.

		Total patients (N=180)	Chronic-stage RCT (N=134)	Acute-stage (N=46)
Demographic information				
Recipient gender (male), N(%)		125 (70)	92 (69)	33 (72)
Body mass index (kg/m2), N(M±SD)		180 (26±5)	134 (27±5)	46 (25±5)
Recipient age at the time of the study (years), N(M±SD)		180 (55±14)	134 (57±14)	46 (51±14)
Patients >75 years old, N(%)		5 (3)	5 (4)	0 (0)
Educational attainment, N(%)	No schooling	21 (12)	15 (11)	6 (13)
	Middle school graduate	80 (44)	58 (43)	22 (48)
	High school graduate	34 (19)	25 (19)	9 (20)
	University graduate	45 (25)	36 (27)	9 (20)
Employment status, N(%)*	Disability	109 (61)	74 (55)	35 (76)
	Currently employed	37 (21)	34 (25)	3 (7)
	Retired	26 (14)	19 (14)	7 (15)
	No previous employment activity	8 (4)	7 (5)	1 (2)
Clinical variables transplant related				
Recipient age at HTx (years), N(M ± SD)		180 (46±15)	134 (45±16)	46 (50±14)
Time from HTx (years)	N(M ± SD)	180 (8±8)	134 (11±7)	46 (0.2±0.4)
	<1.5, N(%)	46 (26)	0 (0)	46 (100)
	>1.5-3; 3-5; 5-10; 10-15, N(%)	17 (9); 7 (4); 27 (15); 36 (20)	17 (13); 11 (18); 27 (20); 36 (27)	0 (0)
	>15, N(%)	43 (24)	43 (32)	0 (0)
Urgent HTx, N(%)		54 (31)	33 (25)	21 (49)
Heart failure etiology, N(%)	Coronary/ischemic	51 (29)	35 (26)	16 (36)
	Cardiomyopathy	78 (44)	60 (45)	18 (40)
	Other	51 (28)	84 (47)	146 (81)
	Re-transplant	10 (6)	8 (6)	2 (4)

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		Total patients (N=180)	Chronic-stage RCT (N=134)	Acute-stage (N=46)
Donor gender (men), N(%)		90 (52)	72 (56)	18 (41)
Donor age, N(M ± SD)		172 (39±15)	128 (36±14)	44 (50±12)
Total ischemia time (min), N(M ± SD)		171 (192±57)	128 (187±57)	43 (208±51)
Mismatch CMV (recipient-/donor+), N(%)		28 (16)	20 (15)	8 (17)
Number of HTxR with at least 1 episode of ARE, N(%)		86 (48)	81 (60)	5 (11)
Number of HTxR with at least 1 episode of AMR, N(%)		7 (4)	7 (5)	0 (0)
CAV >1, N(%)		74 (55)	60 (67)	1 (100)
LVEF (%), N(M±SD)		155 (66±8)	120 (66±8)	35 (67±8)
Multimorbidity and use of care levels of the HTxR included in the study				
Number of comorbidities pre-HTx, N(M±SD)		138 (3±2)	93 (3±2)	45 (4±2)
Number of comorbidities post-HTx, N(M±SD)		170 (6±3)	131 (6±3)	39 (4±2)
Correlation between comorbidities count post-HTx and:	Number of comorbidities pre-HTx (Rho de Spearman)	R=.316 *P*-value=.000	R=.306 *P*-value=.000	R=.708 *P*-value=.000
	Time from HTx (Rho de Spearman)	R=.243 *P*-value=.001	R=.06 *P*-value=.480	R=.00 *P*-value=.975
Need or requirement for caregiver, N(%)		44 (24)	27 (20)	17 (37)
Lives with someone else, N(%)		156 (89)	114 (88)	42 (91)
Medical clinicians, N(M±SD)		146 (3±1)	115 (3±2)	31 (3±1)
Number of patients who were always visited by the same primary care physician, N(%)		160 (90)	121 (90)	39 (89)
Number of primary care visits in the last month, N(%)	None	112 (63)	83 (62)	29 (66)
	1-2 visits	63 (35)	49 (37)	14 (32)
	>3	3 (2)	2 (2)	1 (2)
Reasons for primary care visits, N(%)	Refill prescriptions	89 (54)	60 (48)	29 (73)
	Medical consultation	76 (46)	65 (52)	11 (28)
Number of patients who were always visited by the same pharmacy, N(%)		161 (91)	122 (92)	39 (89)

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		Total patients (N=180)	Chronic-stage RCT (N=134)	Acute-stage (N=46)
Treatment measures				
Immunosuppressive treatment, N(%)	Cyclosporine	35 (19)	33 (25)	2 (4)
	Tacrolimus	142 (79)	98 (73)	44 (96)
	Everolimus	20 (11)	20 (15)	0 (0)
	Sirolimus	3 (2)	3 (2)	0 (0)
	Azathioprine	4 (2)	4 (3)	0 (0)
	Mycophenolate mofetil	103 (57)	71 (53)	32 (70)
	Mycophenolate sodium	40 (22)	29 (22)	11 (24)
	Corticosteroids	160 (89)	114 (85)	46 (100)
Total drugs count, N(M±SD) (Min-Max) IQR		180 (10±3) (3;19) 8;10;13	134 (10±3) (3;18) 7;10;12	46 (13±3) (6;19) 11;12;15
Patients with polypharmacy (≥8 drugs), N(%)		143 (79)	100 (75)	43 (94)
Patients with polypharmacy (≥15 drugs), N(%)		21 (12)	9 (7)	12 (26)
Drugs to treat comorbidities, N(M±SD)		152 (4±2)	115 (4±2)	37 (3±2)
OTC medicies, N(M±SD)		161 (2±1)	125 (2±1)	36 (2±1)
Complementary therapies, N(M±SD)		93 (2±1)	74 (2±1)	19 (2±1)

*No statistically significant differences were found in baseline demographic and clinical variables between the control and intervention group except for employment status (*P*-value=.038).

Abbreviations: AMR, antibody-mediated rejection; ARE, acute cellular rejection episode (Endomyocardial biopsy 1R); BMI, body mass index; CAV, cardiac allograft vasculopathy; CMV, cytomegalovirus; HTx, heart transplantation; HTxR, heart transplant recipients; LVEF, left ventricular ejection fraction; M, mean; OTC, Over The Counter; RCT, Randomized controlled trial; SD, standard deviation.

6.4.2. TECHNOLOGY-RELATED USABILITY AND PREFERENCES

At baseline, 69% of the recipients reported using technology frequently and 97% paying for the Internet (3G or 4G connection). Up to 65% of them had used the Internet to seek health information. A total of 79% of the patients reported that a tool such as mHeart could be "*useful*" or "*very useful*" for them. A quarter (26%) of the patients reported they might need personal assistance to get started using a tool like the mHeart platform. To use an online platform, 86% of the patients might use the app and 61% preferred to combine it with a website (Table 26).

At the end of the study, of 117 patients using mHeart [chronic-stage intervention group N=71; acute-stage N=46], 86% were engaged with mHeart every day, but 6% of them needed to be reminded to use the mHeart platform by the pharmacist at least once during the study period. Of the 14% not using mHeart every day, 3% of recipients reported technical problems, 3% a lack of technology skills, and 6% a lack of interest in using mHeart. None of the participants stopped using mHeart completely (Table 27).

Table 26: Technology-related usability and preferences.

		Total patients (N=180)	Chronic-stage RCT (N=134)	Acute-stage (N=46)
Types of devices owned by patients, N(%)	Computer	132 (74)	97 (73)	35 (78)
	Tablet	77 (43)	60 (45)	17 (38)
	Mobile	177 (98)	131 (98)	46 (100)
Internet access on patients' devices, N(%)	WIFI	27 (15)	18 (13)	9 (20)
	3G or 4G connection	175 (97)	111 (83)	37 (80)
	Does no know/no response	5 (3)	5 (4)	0 (0)
Frequency of technology use, N(%)	Often	124 (69)	87 (65)	37 (80)
	Sometimes	42 (23)	35 (26)	7 (15)
	Never	14 (8)	12 (9)	2 (4)
Internet usage for health-related purposes, N(%)	Often	53 (30)	41 (31)	12 (27)
	Sometimes	63 (35)	43 (32)	20 (44)
	Never	63 (35)	50 (37)	13 (29)
Initial assessment of the mHealth approach for other patients (hypothetical), N(%)	Not very useful	2 (1)	2 (2)	0 (0)
	Useful	117 (65)	91 (68)	26 (57)
	Very useful	60 (33)	40 (30)	20 (44)
	Not yet known until the platform is tested	1 (1)	1 (0.7)	0 (0)
Initial assessment of the mHealth approach for the patient (hypothetical), N(%)	Not very useful	30 (21)	26 (26)	4 (9)
	Useful	84 (58)	57 (58)	27 (59)
	Very useful	30 (21)	16 (16)	14 (30)
	Not yet known until the platform is tested	1 (0.7)	0 (0)	1 (2)
mHeart® type of platform initial assessment, N(%) (multiple choice)	Interested in using mHeart® mobile app	121 (86)	81 (86)	40 (87)
	Interested in using mHeart® website	85 (61)	63 (67)	22 (48)
Initially requires a tutor to use the platform, N(%)		43 (26)	29 (24)	14 (30)

Abbreviations: HTx, heart transplant; RCT, Randomized controlled trial.

Table 27: Recipients' engagement with the mHeart mobile application during the study period according to providers' categorization and patients' agreements with decision.

	Total mHeart patients (N=117)	Chronic-stage RCT IG (N=71)	Acute-stage (N=46)	Patients agreement (%)
Using mHeart every day[a], N(%)	94 (80)	52 (73)	42 (91)	100%
Using mHeart every day but needed assistance[b], N(%)	7 (6)	7 (10)	0 (0)	100%
Not using mHeart every day because technical problems, N(%)	3 (3)	2 (3)	1 (2)	100%
Not using mHeart every day because lack of interest on using mHeart, N(%)	7 (6)	6 (8)	1 (2)	71%
Not using mHeart every day because lack of skills with technology, N(%)	4 (3)	3 (4)	1 (2)	100%
Not using mHeart at all, N(%)	0 (0)	0 (0)	0 (0)	–

[a] All messages received by the team were read on time.

[b] Using mHeart every day but needed to be reminded to use the mHeart platform at least once during the study period.

Abbreviations: IG, RCT Intervention Group; RCT, Randomized controlled trial.

6.4.3. PATIENT-EXPERIENCED OUTCOMES

Patient-experienced outcomes at T_0 and T_1 are detailed in Table 28. Contrast analysis among study groups and visits are detailed in Table 29.

Patient's self-reliance for medication management

As many as 81% of recipients reported being self-reliant for medication management at baseline (T_0) [89% chronic-stage; 59% acute-stage]. A significant improvement was observed for the acute-stage group only at T_2 [*P*-value=.002].

Patient-perceived inconvenience of their medication regimens

The mean medication-related inconvenience at baseline (T_0) was 3 (SD3) (scored 0-10). A significant improvement was observed for the intervention group [*P*-value=.029].

Patient's feeling of taking excessive medication

As many as 67% of recipients believed they were taking excessive medication at baseline (T_0). This percentage was significantly lower at the end of the study (T_2) in the intervention group [OR=4.5 (1.2;17.7), *P*-value=.000].

Patient's opinion of the importance of immunosuppressive treatment and consequences of nonadherence

The analysis of patients' medication beliefs at baseline (T_0) showed that as many as 28% of the patients were unaware of the consequences of completely abandoning immunosuppression therapy, and 7% of the acute-stage recipients believed nothing would happen if they completely stopped taking it. Moreover, 41% of recipients were unaware of the consequences of sometimes forgetting to take their antirejection medicines, and 9% of them believed nothing would happen if they forget them. These percentages were significantly lower at T_2 for the chronic-stage intervention [*P*-value=.000] and control group [*P*-value=<.01], as well as in the acute-stage group [*P*-value=.001].

Patient's knowledge of their regimen

Patients remembered 71% of the names of their medicines (brand or active ingredient), 45% of doses, 76% of intakes and 58% of the drug indications at baseline (T_0). Patients' knowledge of their regimen intakes [*P*-value=.019], drugs names [*P*-value=.006], drugs doses [*P*-value=.030] and drugs indications remembered [*P*-value=.003] significantly improved at the end of the study in the intervention group versus the control group.

Patient-reported medication adverse effects

The mean number of adverse effects reported by patients at baseline (T_0) was 6 (SD3) with a quarter of the recipients reporting 8 or more. The most prevalent were tremor (67%) followed by skin disorders such as rash or acne (51%), visual impairment (49%), feeling too emotional (48%), cramps (45%), mood swings (47%), weakness (45%), headache (40%), and insomnia (34%). The number of adverse effects reported was significantly reduced to 3 (SD2) at the end of the study (T_2) for both the intervention group [*P*-value=.000] and the control group [*P*-value=.000].

Table 28: Patient-experience outcomes.

		Total patients (N=180)			Chronic-stage RCT (N=134)			Acute-stage (N=46)		
Variables		T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
The patient prepares and takes his/her medication autonomously (Yes), N(%)		146 (81)	153 (92)	139 (91)	119 (89)	113 (93)	110 (92)	27 (59)	40 (91)	29 (88)
Person who helps the patient with medication management, N(%)	Partner	16 (70)	5 (39)	6 (46)	4 (50)	2 (25)	3 (43)	12 (80)	3 (60)	3 (50)
	Children	3 (13)	2 (15)	3 (23)	1 (13)	1 (13)	1 (14)	2 (13)	1 (20)	2 (33)
	Caregiver	1 (4)	2 (15)	2 (15)	1 (13)	2 (25)	2 (29)	0 (0)	0 (0)	0 (0)
	Pharmacy office	0 (0)	1 (8)	1 (8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	1 (17)
	Others	3 (13)	3 (23)	1 (8)	2 (25)	3 (38)	1 (14)	1 (7)	0 (0)	0 (0)
Number of patient's feeling of taking excessive medication (Yes), N(%)		119 (67)	75 (45)	63 (41)	82 (63)	53 (43)	47 (39)	37 (80)	22 (50)	16 (47)
Degree of inconvenience perceived by the patient related to taking his/her medication as prescribed every day (scored 0-10)	N(M±SD)	180 (3±3)	167 (2±3)	155 (1±2)	134 (2±3)	123 (2±3)	121 (1±2)	46 (4±3)	44 (3±3)	34 (1±2)
	0-2; 3-6; >7	94 (52); 64 (36); 22 (12)	111 (67); 40 (24); 16 (10)	128 (83); 22 (14); 5 (3)	73 (55); 49 (37); 12 (9)	87 (71); 25 (20); 11 (9)	99 (82); 17 (14); 5 (4)	21 (46); 15 (33); 10 (22)	24 (55); 15 (34); 5 (11)	29 (85); 5 (15)
Patients' awareness of the importance of immunosuppressive therapy and consequences of non-taking it , N(%)										
"If you discontinued taking your immuno-suppressants completely, what do you think would happen to you?"	Nothing	6 (3)	2 (1)	1(0.6)	3 (2)	1(0.8)	0 (0)	3 (7)	1 (2)	1 (3)
	I don't know	44 (25)	19 (11)	2 (1)	34 (26)	16 (13)	2 (2)	10 (22)	3 (7)	0 (0)
	A different answer involving rejection	128 (72)	147 (88)	152 (98)	95 (72)	107 (86)	119 (98)	33 (72)	40 (91)	33 (97)
"If you sometimes forgot to take your immuno-suppressants, what do you think would happen to you?"	Nothing	15 (9)	9 (5)	5 (3)	13 (10)	5 (4)	4 (3)	2 (4.)	4 (9)	1 (3)
	I don't know	57 (32)	41 (24)	12 (8)	41 (31)	34 (27)	10 (8)	16 (35)	7 (16)	2 (6)
	A different answer involving rejection	105 (59)	118 (70)	138 (89)	77 (59)	85 (69)	107 (88)	28 (61)	33 (75)	31 (91)
Knowledge of the therapeutic regimen: % of the number of drugs of the total prescribed, N(M±SD)	Proportion of drugs names remembered	180 (71±33)	168 (82±29)	155 (86±26)	134 (76±29)	124 (80±30)	121 (84±27)	46 (57±39)	44 (88±24)	34 (90±21)
	Proportion of drugs doses remembered	180 (45±30)	168 (54±30)	155 (64±29)	134 (51±29)	124 (53±30)	121 (63±29)	46 (29±27)	44 (58 ±31)	34 (66 ±28)
	Proportion of drugs intakes remembered	180 (76±29)	168 (89±18)	155 (92±19)	134 (79±25)	124 (89±20)	121 (91±21)	46 (66±36)	44 (92±13)	34 (96±12)
	Proportion of drugs indications remembered	180 (58±35)	167 (80±28)	155 (85±23)	134 (62±34)	124 (79±30)	121 (83±24)	46 (46±36)	43 (84±20)	34 (91±16)

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		Total patients (N=180)			Chronic-stage RCT (N=134)			Acute-stage (N=46)		
Variables		T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
Number of medication adverse effects reported by patients, N(M±SD), IQR		180 (6±3), 3;6;8	180 (4±3), 2;4;6	180 (3±2), 1;3;4	134 (6±3), 4;7;8	134 (4±3), 2;4;6	134 (3±2), 2;3;5	46 (5±3), 3;5;8	46 (5±3), 3;5;7	46 (2±2), 0;2;4
Type of medication adverse effects reported by patients, N(%)	Tremor	117 (67)	–	–	79 (62)	–	–	38 (83)	–	–
	Skin disorders	89 (51)	–	–	71 (55)	–	–	18 (39)	–	–
	Visual impairment	82 (49)	–	–	61 (48)	–	–	21 (50)	–	–
	Emotional lability	81 (48)	–	–	63 (49)	–	–	18 (43)	–	–
	Cramps	77 (45)	–	–	63 (49)	–	–	14 (33)	–	–
	Mood swings	79 (47)	–	–	60 (47)	–	–	19 (44)	–	–
	Tiredness or fatigue	77 (45)	–	–	60 (47)	–	–	17 (39)	–	–
	Headache	68 (40)	–	–	53 (41)	–	–	15 (36)	–	–
	Insomnia	59 (34)	–	–	44 (34)	–	–	15 (35)	–	–

Measurement points: T_0 (baseline at inclusion into study), T_1 (at least after 6 months from inclusion), T_2 (at least after 12 months from inclusion).

Abbreviations: HTx, heart transplantation; M, mean; RCT, Randomized controlled trial; SD, standard deviation.

Table 29: Improvement in patient-experience measures over time (T_0 versus T_2) and between the RCT control (CG) and intervention (IG) chronic-stage groups.

Variables		Acute-stage (N=46)	Chronic-stage (N=134)			
			CG (N=63)	IG (N=71)	Statistics OR (IC 95%)	*P*-value
The patient prepares and takes his/her medication autonomously (Yes), N(%)						
▪ T_0	146 (81)	27 (59)	57 (89)	62 (89)	1 (0.3;2.8)	.928*
▪ T_2	139 (91)	29 (88)	49 (89)	61 (94)	1.9 (0.5;7)	.348*
▪ Statistics OR (IC 95%)	49 (9.7;248.3)	—	24 (3;199)	—		
▪ *P*-value McNemar test	.727	**.002**	1	.250		
Number of patient's feeling of taking excessive medication (Yes), N(%)						
▪ T_0	119 (67)	37 (80)	35 (56)	47 (69)	1.79 (0.9;3.7)	.109*
▪ T_2	63 (41)	16 (47)	23 (42)	24 (36)	0.80 (0.4;1.7)	.540*
▪ Statistics OR (IC 95%)	3.8 (1.6;8.9)	1.7 (0.3;8.5)	3.9 (1.2;12.6)	4.5 (1.2;17.7)		
▪ *P*-value McNemar test	**.000**	**.021**	.167	**.000**		
Degree of inconvenience perceived by the patient related to taking his/her medication as prescribed every day (scored 0-10), N(M±SD)						
▪ T_0	180 (3±3)	46 (4±3)	64 (2±2)	70 (3±3)	—	.661*
▪ T_2	155 (1±2)	34 (1±2)	55 (2±3)	66 (0.5±2)	—	**.002***
▪ Statistics OR (IC 95%)	—	—	—	—		
▪ *P*-value T-test	**.000**	**.000**	**.029**	1.94		
Patients' awareness of the importance of immunosuppressive therapy and consequences of non-taking it, N(%)						
1. "If you discontinued taking your immunosuppressants completely, what do you think would happen to you?" (answer 3: rejection)						
▫ T_0	128 (72)	33 (72)	47 (75)	48 (70)	—	.762*
▫ T_2	152 (98)	33 (97)	53 (96)	66 (100)	—	.361
▫ Statistics OR (IC 95%)						
▫ *P*-value Friedman test	**.000**	**.001**	**.001**	**.000**		
2. "If you sometimes forgot to take your immunosuppressants, what do you think would happen to you?" (answer 3: rejection)						
▫ T_0	105 (59)	28 (61)	41 (66)	36 (52)	—	.114*
▫ T_2	138 (89)	31 (91)	47 (86)	60 (91)	—	.201*
▫ Statistics OR (IC 95%)	NA					
▫ *P*-value Friedman test	**.000**	**.001**	**.012**	**.000**		

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Variables		Acute-stage (N=46)	Chronic-stage (N=134)			
			CG (N=63)	IG (N=71)	Statistics OR (IC 95%)	*P*-value
Knowledge of the therapeutic regimen (% of drugs of the total prescribed), N(M±SD)						
▪ Proportion of drugs names remembered						
▫ T_0	180 (71±33)	46 (57±39)	64 (73±33)	70 (79±25)	—	.528**
▫ T_2	155 (86±26)	34 (90±21)	55 (77±32)	66 (91±20)	—	**.006****
▫ *P*-value Wilcoxon test	.183	**.020**	.750	.197		
▪ Proportion of drugs doses remembered						
▫ T_0	180 (45±30)	46 (29±27)	64 (51±32)	70 (50±26)	—	.864**
▫ T_2	155 (64±29)	34 (66 ±28)	55 (56±32)	66 (69±25)	—	**.030****
▫ *P*-value Wilcoxon test	**.043**	**.043**	.842	.072		
▪ Proportion of drugs intakes remembered						
▫ T_0	180 (76±29)	46 (66±36)	64 (81±26)	70 (79±25)	—	.533**
▫ T_2	155 (92±19)	34 (96±12)	55 (87±24)	66 (93±18)	—	**.019****
▫ *P*-value Wilcoxon test	**.033**	.157	.792	.058		
▪ Proportion of drugs indications remembered						
▫ T_0	180 (58±35)	46 (46±36)	64 (58±35)	70 (65±34)	—	.213**
▫ T_2	155 (85±23)	34 (91±16)	55 (77±26)	66 (88±22)	—	**.003****
▫ *P*-value Wilcoxon test	**.001**	**.019**	.284	**.014**		
▪ Number of medication adverse effects reported by patients, N(M±SD)						
▫ T_0	180 (6±3)	46 (5±3)	64 (6±3)	70 (7±3)	—	.294**
▫ T_2	180 (3±2)	46 (2±2)	64 (3±2)	70 (3±2)	—	.799**
▫ *P*-value T-test	**.000**	**.000**	**.000**	**.000**		

Measurement points: T_0 (baseline at inclusion into study), T_2 (at least after 12 months from inclusion).

*Pearson's chi-squared test ($\chi 2$); **Wilcoxon Test.

Abbreviations: HTx, heart transplantation; M, mean; SD, standard deviation; GI, RCT intervention group; CG, RCT control group; OR, Odds Ratio; RCT, Randomized controlled trial.

6.4.4. MEDICATION ADHERENCE RATES

adherence to medication rates at T_0, T_1, T_2 are detailed in Table 30. Before randomization, 36% of recipients were adherent to the immunosuppressive treatment according to the SMAQ interview questionnaire [29% chronic-stage group; 57% acute-stage group]. The BAASIS patient self-reported questionnaire showed 65% of adherence to antirejection [59% chronic-stage group; 88% acute-stage group]. On the Haynes-Sackett scale, 71% of recipients were adherent to co-medication [69% chronic-stage group; 74% acute-stage group]. The composite adherence score showed that only 15% of recipients were considered fully adherent [14% chronic-stage group; 18% acute-stage group]. The intervention effects on MNA rates are provided in Table 31.

Self-report

At T_2 nonadherence rates improved significantly from baseline in the intervention group (65%) according to the Global SMAQ interview questionnaire [OR=2.3 (0.3;19.7), *P*-value=.000]. Time-scheduled drugs (IMTS test) also significantly improved [OR=4.2 (0.5;37.5), *P*-value=.000] and the Global BAASIS patient self-reported questionnaire showed a tendency to improve in these group [OR=6.2 (1.4;27.9), *P*-value=.057]. The VAS score (BAASIS) for patient self-reported feeling of adequate therapy management significantly improved in the intervention group [*P*-value=.033].

Assay

Variability for tacrolimus and cyclosporine was high during the study period. A CV>30% was observed in 49% of recipients [47% CG; 41% IG, *P*-value=.526], while SD>2 was observed in 56% of recipients [53% CG; 43% IG, *P*-value=.235]. The mean number of supratherapeutic levels for tacrolimus was significantly lower in the intervention group [*P*-value=.040]. Subtherapeutic levels were also less frequent in the IG, but this improvement was not significant [*P*-value=.572].

Co-medication

The Haynes-Sackett self-reported scale comparison at T_2 showed a significant improvement in co-medication adherence in the intervention group [OR=1.5 (0.1;24.4), *P*-value=.000]

Number of missing visits

Adherence to in-clinic appointments was significantly reduced at T_2 in the entire sample [*P*-value=.002], but this difference was not observed in any group.

Composite adherence score

A significant improvement in medication adherence rates was observed at T_2 in the intervention group [*P*-value<.001] and between groups [OR=0.3 (0.1;0.6), *P*-value=.001].

Table 30: Adherence to medication rates.

		Total patients (N=180)			Chronic-stage RCT (N=134)			Acute-stage (N=46)		
Variables		T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
Haynes Sackett (Adh), N(%)	"Most patients have difficulty taking all their tablets. Do you have difficulties taking yours?" (No)	127 (71)	138 (83)	142 (92)	93 (69)	104 (85)	110 (91)	34 (74)	34 (77)	32 (94)
SMAQ Global (Adh.), N(%)	Sum of participants answering 1=yes and/or 2=no and/or 3=no and/or 4= no and/or 5= never	64 (36)	77 (46)	111 (72)	38 (29)	55 (45)	81 (67)	26 (57)	22 (50)	30 (91)
SMAQ 1, N(%)	"Do you always take your medication at the appropriate time?" (Yes)	112 (68)	100 (72)	128 (88)	79 (63)	69 (68)	97 (85)	33 (83)	31 (84)	31 (97)
SMAQ 2, N(%)	"When you feel bad, have you ever discontinued taking your medication?" (Yes)	20 (12)	9 (7)	4 (3)	20 (16)	8 (8)	3 (3)	0 (0)	1 (3)	1 (3)
SMAQ 3, N(%)	"Have you ever forgotten to take your medication?" (Yes)	91 (55)	55 (40)	28 (19)	79 (63)	41 (40)	27 (24)	12 (30)	14 (38)	1 (3)
SMAQ 4, N(%)	"Have you ever forgotten to take your medication during the weekend?" (Yes)	19 (12)	11 (8)	7 (5)	14 (11)	9 (9)	6 (5)	5 (13)	2 (5)	1 (3)
SMAQ 5, N(%)	"In the last week, how many times did you fail to take your prescribed dose?"									
	▪ Never	153 (85)	148 (88)	135 (87)	111 (83)	110 (89)	102 (84)	42 (91)	38 (86)	33 (97)
	▪ 1-2 times	25 (14)	16 (10)	14 (9)	22 (16)	11 (9)	13 (11)	3 (7)	5 (11)	1 (3)
	▪ 3-5 times	2 (1)	2 (1)	2 (1)	1 (0.7)	1 (0.8)	2 (2)	1 (2)	1 (2)	0 (0)
	▪ 6-10 times	0 (0)	1 (0.6)	3 (2)	0 (0)	1 (0.8)	3 (3)	0 (0)	0 (0)	0 (0)
	▪ >10 times	0 (0)	1 (0.6)	1 (0.6)	0 (0)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)
SMAQ 6, N(M±SD)	"Since your last visit, how many whole days have gone by in which you did not take your medication?"	173 (1±1)	165 (0.6±1)	152 (0.5±2)	128 (0.5±1)	121 (0.5±1)	118 (0.6±2)	45 (0.3±0.7)	44 (0.6±2)	34 (0.1±0.3)
IMTS Global (Adh.), N(%)	Sum of participants answering "*No*" to questions 1 and 2	93 (52)	104 (63)	127 (83)	59 (44)	71 (58)	98 (82)	34 (76)	33 (79)	29 (88)
IMTS (1), N(%)	"Did you modify the immunosuppressant timetable in the last week?"									
	▪ No	111 (62)	113 (67)	129 (83)	75 (56)	75 (61)	99 (82)	36 (78)	38 (86)	30 (88)
	▪ >once	68 (38)	54 (32)	26 (17)	58 (43)	48 (39)	22 (18)	10 (22)	6 (14)	4 (12)
	▪ I don't remember	1 (1)	1 (0.6)	0 (0)	1 (0.7)	1 (0.8)	0 (0)	0 (0)	0 (0)	0 (0)
IMTS (2), N(%)	"Did you modify the immunosuppressant timetable since the last visit?"									
	▪ No	94 (52)	105 (63)	127 (82)	60 (45)	71 (57)	97 (80)	34 (74)	34 (77)	30 (88)
	▪ >once	40 (22)	31 (19)	16 (10)	34 (25)	26 (21)	15 (12)	6 (13)	5 (11)	1 (3)
	▪ >5 times	45 (25)	31 (19)	11 (7)	39 (29)	26 (21)	8 (7)	6 (13)	5 (11)	3 (9)
	▪ I don't remember	1 (1)	1 (0.6)	1 (0.6)	1 (0.7)	1 (0.8)	1 (0.8)	0 (0)	0 (0)	0 (0)
BAASIS Global (Adh.), N(%)	Sum of participants answering "*No*" to questions 1a, 1b, 2, and 3	92 (65)	85 (73)	89 (69)	64 (59)	62 (71)	69 (70)	28 (88)	23 (79)	20 (67)

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Variables		Total patients (N=180)			Chronic-stage RCT (N=134)			Acute-stage (N=46)		
		T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
BAASIS (1a) Taking dimension, N(%)	"Do you remember missing a dose of your IM in the past 4 weeks?" (yes)	23 (15)	15 (12)	9 (7)	18 (16)	11 (12)	7 (7)	5 (14)	4 (13)	2 (7)
	▪ 1 time	8 (47)	8 (47)	5 (50)	13 (68)	6 (46)	4 (50)	4 (67)	2 (50)	1 (50)
	▪ 2 times	7 (41)	7 (41)	4 (40)	4 (21)	5 (39)	3 (38)	2 (33)	2 (50)	1 (50)
	▪ 3 times	2 (12)	2 (12)	0 (0)	0 (0)	2 (15)	0 (0)	0 (0)	0 (0)	0 (0)
	▪ 4 times	0 (0)	0 (0)	1 (10)	0 (0)	0 (0)	1 (13)	0 (0)	0 (0)	0 (0)
	▪ >4 times	0 (0)	0 (0)	0 (0)	2 (11)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BAASIS (1b) Drug holidays, N(%)	"Do you remember having skipped two or more doses of your IM in a row in the past 4 weeks?" (yes)	4 (11)	4 (19)	3 (14)	3 (10)	3 (19)	2 (13)	1 (14)	1 (20)	1 (17)
	▪ 1 time	3 (50)	3 (38)	0 (0)	3 (60)	3 (50)	0 (0)	0 (0)	0 (0)	0 (0)
	▪ 2 times	1 (17)	5 (63)	3 (100)	0 (0)	3 (50)	2 (100)	1 (100)	2 (100)	1 (100)
	▪ 3 times	1 (17)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	▪ 4 times	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	▪ >4 times	1 (17)	0 (0)	0 (0)	1 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
BAASIS (2) Timing dimension, N(%)	"Do you remember having taken your IM more than 2 hours before or after the prescribed dosing time in the past 4 weeks?" (yes)	38 (26)	29 (23)	38 (30)	36 (32)	22 (24)	28 (28)	2 (6)	7 (22)	10 (33)
	▪ 1 time	11 (30)	15 (56)	12 (38)	9 (26)	11 (52)	8 (32)	0 (0)	0 (0)	0 (0)
	▪ 2-3 times	15 (41)	9 (33)	17 (53)	15 (43)	7 (33)	14 (56)	0 (0)	0 (0)	0 (0)
	▪ 4-5 times	5 (14)	1 (4)	3 (9)	5 (14)	1 (5)	3 (12)	0 (0)	0 (0)	0 (0)
	▪ Every 2 to 3 days	2 (5)	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	▪ Almost everyday	4 (11)	2 (7)	0 (0)	4 (11)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)
BAASIS (3) Reduction of dose, N(%)	"Have you altered the prescribed amount of your IM during the past 4 weeks without your doctor telling you to do so?" (yes)	1 (0.7)	2 (2)	4 (3)	1 (0.9)	2 (2)	2 (2)	0 (0)	0 (0)	2 (7)
BAASIS (4). Persistence, N(%)	"Have you stopped taking your IM completely in the past 4 weeks without your doctor telling you to do so?" (yes)	1 (0.7)	1 (0.8)	0 (0)	1 (0.9)	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
Baasis (5). VAS Scale, N(M±SD)	Patients' referred overall adherence past 4 weeks (score 0 to 100)	148 (94±14)	124 (95±12)	128 (96±8)	113 (93±14)	92 (95±13)	98 (95±8)	35 (97±10)	32 (97±7)	30 (96±7)
Adherence to visits, N(%)		179 (99)	167 (93)	154 (86)	133 (99)	123 (92)	121 (90)	46 (100)	44 (96)	33 (72)

Measurement points: T_0 (baseline at inclusion into study), T_2 (at least after 12 months from inclusion).

Abbreviations: Adh., adherence to medication; Basel Assessment of Adherence to Immunosuppressive Medications Scale (BAASIS); GI, RCT intervention group; CG, RCT control group; HTx, heart transplantation; Immunosuppressive Medication (IM); Immunosuppressive Medication Timing Scale (IMTS); M, mean; Nonadh., Nonadherence to medication; OR, Odds Ratio; RCT, Randomized controlled trial; Simplified Medication Adherence Questionnaire (SMAQ); SD, standard deviation; Visual Analog Scale (VAS).

Table 31: Medication adherence improvement over time (T_0 versus T_2) and between the RCT control (CG) and intervention (IG) chronic-stage groups.

Variables	Total patients (N=180)	Acute-stage (N=46)		Chronic-stage RCT (N=134)			
				CG (N=63)	IG (N=71)	Statistics OR (IC 95%)	*P*-value
Self-report							
Haynes Sackett (Adh), N(%)							
▪ T_0	127 (71)	34 (74)		52 (81)	41 (59)	0.3 (0.2;0.7)	**.004***
▪ T_2	142 (92)	32 (94)		46 (84)	64 (97)	6.3 (1.3;30.4)	**.011***
▪ Statistics OR (IC 95%)	0.8 (0.2;3.2)	—		1.1 (0.2; 6.6)	1.5 (0.1;24.4)		
▪ *P*-value McNemar test	**<.001**	**.013**		.804	**.000**		
SMAQ Global (Adh.), N(%)							
▪ T_0	64 (36)	26 (57)		24 (38)	14 (20)	0.4 (0.2;0.9)	**.028***
▪ T_2	111 (72)	30 (91)		25 (46)	56 (85)	6.7 (2.9;15.8)	**.000***
▪ Statistics OR (IC 95%)	1.3 (0.5;3.2)	—		2.2 (0.7; 6.7)	2.3 (0.3;19.7)		
▪ *P*-value McNemar test	**<.001**	**.003**		.286	**.000**		
IMTS Global (Adh.), N(%)							
▪ T_0	93 (52)	34 (76)		32 (51)	27 (39)	0.6 (0.3;1.2)	.157*
▪ T_2	127 (83)	29 (88)		40 (73)	58 (89)	3.1 (1.2;8.3)	**.020***
▪ Statistics OR (IC 95%)	3.1 (1.1;9.2)	0.6 (0.1;6.9)		3.7 (1.0;13.7)	4.2 (0.5;37.5)		
▪ *P*-value McNemar test	**<.001**	.092		**.007**	**.000**		
BAASIS Global (Adh.), N(%)							
▪ T_0	92 (65)	28 (88)		34 (63)	30 (55)	1.4 (0.7;3.1)	.372*
▪ T_2	89 (69)	20 (67)		30 (64)	39 (75)	0.6 (0.3;1.4)	.227*
▪ Statistics OR (IC 95%)	7.4 (2.7;20.4)	2.7 (0.1;49.8)		12 (2.6;54.2)	6.2 (1.4;27.9)		
▪ *P*-value McNemar test	.210	.125		1.0	.057		
BAASIS (4). Persistence, N(%)							
▪ T_0	1 (0.7)	0 (0)		0 (0)	1 (2)	—	.319*
▪ T_2	0 (0)	0 (0)		0 (0)	0 (0)	—	—
▪ Statistics OR (IC 95%)	—	—		—	—		
▪ *P*-value McNemar test	—	—		—	—		
Baasis (5). VAS Scale, N(M±SD)							
▪ T_0	148 (94±14)	35 (97±10)		56 (93±13)	57 (93±16)	—	.672**
▪ T_2	128 (96±8)	30 (96±7)		46 (95±7)	52 (96±9)	—	.225**
▪ Statistics OR (IC 95%)	—	—		–	–		
▪ *P*-value Friedman test	.639	.166		.739	**.033**		

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Variables	Total patients (N=180)	Acute-stage (N=46)		Chronic-stage RCT (N=134)			
				CG (N=63)	IG (N=71)	Statistics OR (IC 95%)	*P*-value
Adherence to visits, N(%)							
▪ T_0	179 (99)	46 (100)		64 (100)	69 (99)	_	.337*
▪ T_2	154 (86)	33 (72)		55 (86)	66 (94)	0.37 (0.1;1.3)	.103*
▪ Statistics OR (IC 95%)	—	—		—	—		
▪ *P*-value McNemar test	**.002**	—		—	.375		
Assay result variability							
Drug level ng/ml, N(mean±SD)							
▪ Cyclosporine	33 (137±33)	2 (175±27)		16 (140±30)	15 (129±35)	—	.356****
▪ Tacrolimus	146 (8±2)	43 (10±2)		48 (7±2)	55 (7±2)	—	.943****
CV%, N(mean±SD)							
▪ Total	179 (33±18)	45 (37±16)		64 (34±22)	70 (29±15)	—	.392**
▪ Cyclosporine	33 (30±17)	2 (30±23)		16 (32±17)	15 (28±19)	—	.468****
▪ Tacrolimus	146 (33±18)	43 (37±15)		48 (34±24)	55 (29±14)	—	.615**
CV% >30%, N(%)							
▪ Total	87 (49)	28 (62)		30 (47)	29 (41)	—	.526***
▪ Cyclosporine	15 (46)	1 (50)		8 (50)	6 (40)	—	.722***
▪ Tacrolimus	72 (49)	27 (63)		22 (46)	23 (42)	—	.682***
SD >2.5, N(%)							
▪ Total	100 (56)	36 (80)		34 (53)	30 (43)	—	.235***
▪ Cyclosporine	32 (97)	2 (100)		16 (100)	14 (93)	—	.484***
▪ Tacrolimus	68 (47)	34 (79)		18 (38)	16 (29)	—	.365***
Sub-therapeutic blood levels, N(mean±SD)							
▪ Total	126 (3±3)	29 (3±3)		48 (4±4)	49 (3±2)	—	.251**
▪ Cyclosporine	31 (5±3)	1 (5±0)		16 (6±4)	14 (4±2)	—	.141**
▪ Tacrolimus	95 (3±3)	28 (3±3)		32 (3±3)	35 (2±2)	—	.572**
Supra-therapeutic blood levels, N(mean±SD)							
▪ Total	83 (4±4)	40 (5±4)		23 (4±4)	20 (2±4)	—	**.050****
▪ Cyclosporine	4 (1±0.5)	0 (0)		3 (1±1)	1 (1±0)	—	.564**
▪ Tacrolimus	79 (4±4)	40 (5±4)		20 (4±4)	19 (2±4)	—	**.040****
Therapeutic blood levels, N(%)							
▪ Total	25 (14)	1 (2)		11 (17)	13 (19)	—	**.000*****
▪ Cyclosporine	2 (6)	1 (50)		0 (0)	1 (7)	—	.294***
▪ Tacrolimus	23 (16)	0 (0)		11 (23)	12 (22)	—	.894***

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Variables	Total patients (N=180)	Acute-stage (N=46)		Chronic-stage RCT (N=134)			
				CG (N=63)	IG (N=71)	Statistics OR (IC 95%)	*P*-value
Composite adherence score, N(%)							
▪ T_0	27 (15)	8 (18)		13 (20)	6 (9)	—	.052***
▪ T_2	60 (34)	9 (20)		15 (23)	36 (51)	0.3 (0.1;0.6)	**.001*** **
▪ *P*-value McNemar test	**<.001**	1.000		0.791	**<.001**		

See variables and methods section for definitions. Measurement points: T_0 (baseline at inclusion into study), T_2 (at least after 12 months from inclusion).

*Pearson's chi-squared test (χ2); **Mann–Whitney U-test (exact sig 2-tailed); ***χ2 Test (Fisher exact test 2-tailed); ****T-Test (exact sig 2-tailed)

Abbreviations: Adh., adherence to medication; BAASIS, Basel Assessment of Adherence to Immunosuppressive Medications Scale; GI, RCT intervention group; CG, RCT control group; CV, Coefficient of Variability; HTx, heart transplantation; IM, Immunosuppressive Medication; IMTS, Immunosuppressive Medication Timing Scale; M, mean; Nonadh., Nonadherence to medication; OR, Odds Ratio; RCT, Randomized controlled trial; SMAQ, Simplified Medication Adherence Questionnaire; SD, standard deviation; VAS, Visual Analog Scale.

6.4.5. IN-CLINIC PERSONALIZED INTERVENTIONS BY THE PHARMACIST TO IMPROVE PATIENTS' MEDICATION MANAGEMENT

A mean of 4 (SD2) person-centered interventions to improve patients' medication self-management were performed by the pharmacist during in-clinic appointments. Details are provided in Table 32, the most frequent were the following: interactions were checked in 76% of recipients, use of a pillbox was recommended in 56% of them, at least 1 therapy optimization intervention to reduce therapeutic complexity was conducted in 69% of the recipients, and a written regimen timetable was given to 27% of the patients.

Table 32: Prevalence of in-clinic personalized interventions by the pharmacist to improve patients' medication management.

	Total patients (N=180)			Chronic-stage RCT (N=134)			Acute-stage (N=46)		
Variables	T_0	T_1	T_2	T_0	T_1	T_2	T_0	T_1	T_2
Number of patient-centered interventions during on-site visits, N(M±SD)	180(4±2)	180(3±2)	180(2±2)	134(3±1)	134(3±2)	134(2±2)	46(4±2)	46(4±2)	46(3±2)
To recommend a self-managed pillbox, N(%)	101 (56)	39 (23)	29 (19)	81 (60)	28 (23)	24 (20)	20 (44)	11 (25)	5 (15)
To recommend a pillbox pharmacy office made, N(%)	5 (3)	2 (1)	1 (0.6)	3 (2)	0 (0)	0 (0)	2 (4)	2 (5)	1 (3)
To assess pill count at the next in-clinic appointment, N(%)	1 (0.6)	2 (1)	1 (0.7)	1 (0.7)	0 (0)	0 (0)	0 (0)	2 (5)	1 (3)
To contact the primary care physician or the pharmacy office, N(%)	5 (3)	12 (7)	10 (7)	3 (2)	11 (9)	9 (8)	2 (4)	1 (2)	1 (3)
To contact the social worker because of financial problems, N(%)	3 (2)	3 (2)	2 (1)	0 (0)	1 (0.8)	1 (0.8)	3 (7)	2 (5)	1 (3)
To receive a written regimen timetable, N(%)	47 (27)	15 (9)	10 (7)	20 (15)	7 (6)	6 (5)	27 (63)	8 (18)	4 (12)
Optimization interventions to reduce therapeutic complexity[a], N(%)	123 (69)	107 (65)	74 (48)	94 (71)	75 (62)	47 (39)	29 (64)	32 (73)	27 (79)
To check for drug-drug, drug-disease or herbal-drug interactions, N(%)	135 (76)	120 (73)	107 (70)	103 (78)	88 (73)	82 (68)	32 (71)	32 (73)	25 (74)

Measurement points: T_0 (baseline at inclusion into study), T_1 (at least after 6 months from inclusion), T_2 (at least after 12 months from inclusion).

[a] Therapy optimization strategies based on previously published suggested interventions according to the therapeutic complexity observed in our HTx population. (Appendix 5)

Abbreviations: HTx, heart transplantation; M, mean; RCT, Randomized controlled trial; SD, standard deviation.

The need for in-clinic interventions performed by the pharmacist significantly decreased at T_2 in all patients' groups [*P*-value=.000]. Therapeutic complexity management was improved at the end of the study (T_2) since the total number of *drugs to treat comorbidities* [*P*-value=.000] and the number of over-the-counter medications [*P*-value=.063] was reduced in the IG. (Table 33)

Table 33: In-clinic personalized interventions by the pharmacist and medication management improvement over time (T_0 versus T_2) and between the RCT control (CG) and intervention (IG) chronic-stage groups.

	Total patients (N=180)	Acute-stage (N=46)	Chronic-stage RCT (N=134)		
			CG (N=63)	IG (N=71)	*P*-value
Number of patient-centered interventions during on-site visits, N(M±SD)					
▪ T_0	180 (4±2)	46 (4±2)	63 (3±1)	71 (4±1)	**.027***
▪ T_2	180 (2±2)	46 (3±2)	63 (2±2)	71 (2±2)	.172*
▪ *P*-value T-test	**.000**	**.003**	**.000**	**.000**	
Drugs to treat comorbidities, N(M±SD)					
▪ T_0	180 (4±2)	46 (3±2)	63 (3±2)	71 (3±3)	.551*
▪ T_2	180 (3±2)	46 (2±2)	63 (3±3)	71 (2±2)	.337*
▪ *P*-value T-test	**.001**	**.001**	.176	**.000**	
Over the Counter (OTC) medication, N(M±SD)					
▪ T_0	146 (2±1)	21 (2±1)	60 (2±1)	65 (2±1)	.418*
▪ T_2	115 (2±1)	21 (1±1)	42 (2±1)	52 (2±1)	.806*
▪ *P*-value T-test	**.016**	**.002**	.124	**.063**	
Complementary therapies, N(M±SD)					
▪ T_0	83 (3±2)	9 (1±0.4)	32 (2±1)	42 (2±1)	.792*
▪ T_2	60 (3±1)	9 (3±2)	21 (2±1)	30 (3±2)	.161*
▪ *P*-value T-test	.733	.056	.607	.500	

See variables and methods section for definitions. Measurement points: T_0 (baseline at inclusion into study), T_2 (at least after 12 months from inclusion).

* Pearson's chi-squared test ($\chi 2$).

Abbreviations: GI, RCT intervention group; CG, RCT control group; HTx, heart transplantation; M, mean; Nonadh., Nonadherence to medication; OR, Odds Ratio; RCT, Randomized controlled trial; SD, standard deviation.

6.4.6. INTENSITY OF THE TREATMENT AND IN-CLINIC APPOINTMENTS WITH THE CLINICAL PHARMACIST

Because of the possibility of online follow-up, patients' in-clinic appointment needs with the clinical pharmacist and the intensity of the follow-up at the end of the study (T_2) were significantly reduced in the intervention group [OR=3.4 (1.7;6.9), *P*-value=.001]. Patients' need for in-clinic appointments with the clinical pharmacist in the control group was 65% compared with 35% of recipients in the IG. Details about follow-up intensity after the end of the study are detailed in Table 34.

Table 34: Intensity of the treatment and in-clinic appointments with the clinical pharmacist for medication management follow-up at the end of the study.

	Chronic-stage RCT (N=134)			Acute-Stage (N=46)
	CG (N=63)	IG (N=71)	*P*-value	
No need for regular face-to-face in-clinic appointments, N(%)				
Total	22 (35)	46 (65)	**<.001***	22 (48)
Discharge from in-clinic visits	22 (35)	19 (27)	—	19 (41)
Discharge with intensive mHeart reminders to track medication adherence	0 (0)	18 (25)	—	3 (7)
Discharge with mHeart reminders to follow lifestyle habits affecting medication regimens	0 (0)	9 (13)	—	0 (0)
Need for regular face-to-face in-clinic appointments, N(%)				
Total	41 (65)	25 (35)	**<.001***	24 (52)
Intensive in-clinic follow-up every 6 months	7 (11)	3 (4)	—	5 (11)
Annual in-clinic follow-up to reinforce medication adherence	28 (44)	14 (20)	—	10 (22)
Annual in-clinic follow-up for other medication-related issues	6 (10)	8 (11)	—	9 (20)

*Pearson's chi-squared test ($\chi 2$).

Abbreviations: RCT, Randomized controlled trial.

DISCUSSION

7. DISCUSSION

MAIN FINDINGS OF *THE MHEART STUDY*

The relevant findings enclosed in this thesis work, *The mHeart Study*, were obtained from 4 studies. First, multimorbidity in chronic-stage HTx was alarmingly high, with an average of 6 chronic comorbidities. In addition, therapeutic complexity, measured as the *total pMRCI-S score*, was the highest than that reported in previous studies in chronic diseases. Multivariate analysis showed that this finding was mainly due to a higher count of *drugs to treat comorbidities*.

The quantitative index pMRCI score was found to be a sensitive method allowing identification of the factors determining therapeutic complexity post-HTx. This could help health providers to select strategies to reduce pMRCI-S values. Furthermore, the high multimorbidity and therapeutic complexity observed confirmed the need for feasible strategies to improve health outcomes in the HTx population.

Second, a holistic mHealth-based interventional model to improve medication management and clinical care in high complex populations was successfully developed and implemented in the HTx population in the ambulatory setting. The clinical intervention was supported by the design of a new tool, the mHeart system. Digital behavior change interventions were designed to promote the change on patients' patterns, co-responsibility and self-empowerment. Moreover, the mHeart features were developed to increase the opportunities for patient-providers' interactions.

The HTx recipients included in this study confirmed that almost all of the patients had access to smartphones, and most importantly, they were willing to use the mHeart system. The model implementation was costly and time-consuming and its generalizability into usual care practice entailed several barriers. We experienced that a multidisciplinary healthcare team, experts from various fields, scientific societies and patient associations were

essential to meet the quality requirements and the scalability of the model. Moreover, the clinical pharmacists' skills on patient engagement, motivational interviewing and managerial were essential to lead the implementation.

Third, the mHeart approach was validated in a pilot exploratory study including acute-stage HTx recipients. The mHeart electronic questionnaires proved to be as equally effective as the traditional on-site method in identifying nonadherent recipients. Moreover, the multilevel behavioral change intervention established in an exploratory study (*the mHeart strategy*) has been considered highly effective since the improvement in medication adherence was 30%, higher than previous studies. Patients adhered well to the study protocol and provided excellent feedback; overall satisfaction with the mHeart approach was 9 (score 0-10) and 100% of the patients would recommend it to other recipients. Patients highlighted personalized communication, support from professionals, and self-empowerment as the most relevant benefits of the mHeart interventional program.

Finally, *The mHeart study* went further beyond these 3 studies, and a long-term randomized clinical trial was performed in a representative sample of the chronic-stage HTx population. The intensive follow-up program based on the already validated mHeart Strategy had a positive impact on the prespecified outcomes measured. Patients' experience of therapeutic regimens significantly improved with *the mHeart strategy*. This included a 50% reduction in adverse effects; feeling of taking excessive medication was reduced in a third of recipients; more than 90% the drug intakes were remembered; and almost all the patients were aware of the impact of not taking immunosuppressive medication.

The multifaceted intervention to improve medication adherence was highly effective since immunosuppressive medication significantly improved by 65% in the intervention group according to the SMAQ questionnaire. Finally, *the mHeart strategy* had reduced the number of patients needing to travel to the clinic for pharmaceutical care follow-up appointments by 65%. Therefore,

mHealth technology facilitated a modern way of providing advanced individually-tailored interventions by their health providers in the at-home setting.

Other relevant implications and future lines are emerging from the thesis work. The implementation of a behavioral change technology model targeting HTx population in our center demanded a multidisciplinary approach. The implementation of *The mHeart Study* by the Pharmacy Department provided an opportunity to make the clinical pharmacy visible to patients, families and institutions. In addition, mHealth practice was an excellent opportunity to expand the benefits of pharmaceutical care in the health care system.

The transition from an innovation project to an established practice was a priority for the *The mHeart Study*. This entailed funding and organization adjustments led by the Pharmacy Department and the Heart Transplant Unit and also required input from patients, providers and institutions. Moreover, the mHeart model is being applied to other chronic populations in the Institution and has been used by many other centers to develop their own version of the software.

Therefore, the implications of this thesis research and the eHealth model established may be a promising starting point for an already emerging way of providing further assistance to the most complex populations based on eHealth by the Health Systems.

7.1. STUDY 1. MULTIMORBIDITY AND MEDICATION COMPLEXITY: NEW CHALLENGES IN HEART TRANSPLANTATION

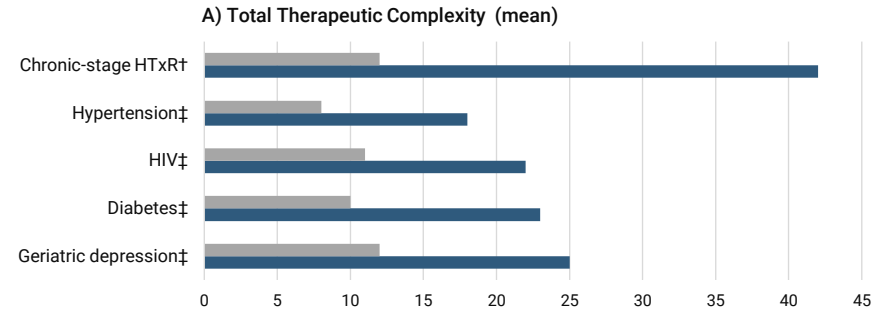
7.1.1. PRINCIPAL FINDINGS

This study is focused on quantifying the already known complexity of long-term HTx survivors and on identifying its risk factors. These will in turn allow further strategies to help reduce the impact of the complexity on post-HTx outcomes.

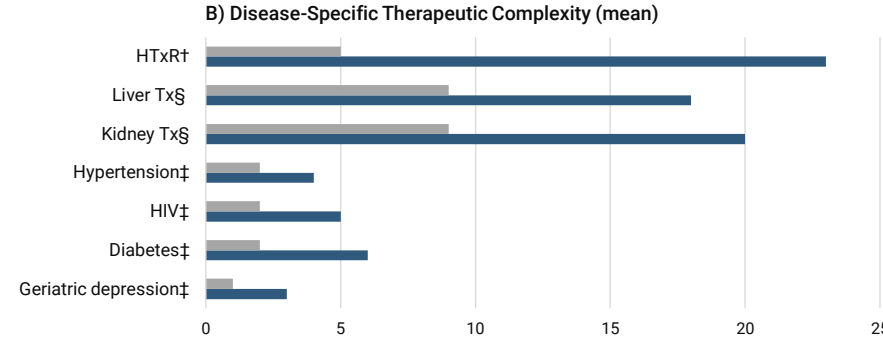
In this study, multimorbidity was found in almost all HTx recipients with an average of 6 chronic comorbidities, most of them new-onset, treated with lifetime use of 7 drugs. Furthermore, the pMRCI-S score in our cohort was 42, while Libby et al. (39) reported pMRCI scores of 18, 22, 23 and 25 in hypertension, HIV infection, diabetes mellitus, and geriatric patients with depression, respectively.

Therefore, the pMRCI-S score obtained suggests that although the HTx population take the same number of prescribed drugs (Figure 29A) such as those with other diseases, (39) they have the highest levels of therapeutic complexity.

Figure 29: Comparison of therapeutic complexity observed in our study and that reported in different chronic diseases.



	Geriatric depression‡	Diabetes‡	HIV‡	Hypertension‡	Chronic-stage HTxR†
Total medication count	12	10	11	8	12
Total pMRCI-S Score	25	23	22	18	42



	Geriatric depression‡	Diabetes‡	HIV‡	Hypertension ‡	Kidney Tx§	Liver Tx§	HTxR†
Disease-specific medication count	1	2	2	2	9	9	5
Disease pMRCI-S score	3	6	5	4	20	18	23

(A) Total therapeutic complexity. The *total pMRCI-S score* in chronic-stage HTx recipients in our study† was higher than the pMRCI observed by Libby et al.‡ (39) in chronic diseases treated with a similar total number of prescribed drugs (hypertension, HIV, diabetes, geriatric depression).

(B) Specific disease therapeutic complexity in our study† was similar to that observed in liver and kidney transplant.§ (38) Solid organ transplant disease-specific therapeutic complexity was at least 3 times higher than the scores observed in other prevalent chronic diseases (hypertension, HIV, diabetes, geriatric depression).‡ (39)

Abbreviations: HTxR, heart transplant recipients; pMRCI, patient Medication Regimen Complexity Index; pMRCI-S, patient Medication Regimen Complexity Index Spanish Version.

In our experience, the pMRCI-S score is a novel method which has been proved to be sensitive to quantify and identify individual causes of therapeutic complexity in long-term HTx recipients. To the best of our knowledge, this is the first study that identifies factors predictive of higher complexity levels in the HTx recipients. In line with previous studies, (46,224) the medication category *drugs to treat comorbidities* was related to higher therapeutic complexity. Most importantly, this was the only medication category related to the same variables such as the *total pMRCI-S Score* (adverse effects, comorbidities, and disability among others) and also showed the same correlation with solid organ malignancies and renal function.

The low intra-patient variability in therapeutic complexity measures for *immunosuppressant* category confirm that antirejection regimens are similar for all the chronic-stage HTx recipients included. *Drugs to treat comorbidities*, however, showed very high variability influenced by the number of comorbidities post-HTx. Therefore, even if *immunosuppression* category can be improved (using prolonged-release presentations, scheduling drugs with meals, or many other relevant strategies described in Appendix 5), the large margin of complexity optimization in the long-term survivors in our study lies in *drugs to treat comorbidities* regimens.

Of interest, therapeutic complexity was strongly related to patients' experience and beliefs about medication, in line with the findings of other studies. (49–51) A third of the HTx recipients included were unaware of the impact of nonadherence to immunosuppression therapy and more than a half believed that their regimen was excessive. Urgent interventions are required post-HTx, since lack of knowledge on medication increases the risk of MNA, (18,56) poor health outcomes, and high economic costs. (15,17,28,56,62,76)

7.1.2. CLINICAL APPLICABILITY OF THE PMRCI SCORE IN THE HEART TRANSPLANT POPULATION

In this study, we tested the use of the pMRCI-S, a widely validated method, in HTx clinical practice. The pMRCI-S has advantages over considering only the number of prescribed drugs in HTx population. First, the pMRCI-S subcategories provide valuable information about which regimen factors are most closely related to higher therapeutic complexity scores. This information will allow professionals to tailor medication management interventions in order to reduce the index rates and optimize medication regimens in HTx recipients. (59)

Second, like other authors, (39,48) we found that this index is sensitive in discriminating different risk values of therapeutic complexity. Therefore, recipients in need of interventions may be prioritized. In previous studies, pMRCI score cut-off values of 33-35 predicted hospital readmission, among other negative consequences of therapeutic complexity in elderly patients. (48) In adult outpatients, a cut-off value of 24 has been proposed as a predictive factor for the need for clinicians to optimize therapy and reduce its burden. (48) However, in our study, higher pMRCI-S predictive values were observed, since a pMRCI-S cut-off value of 40 and 53 best discriminated poor renal dysfunction and risk of malignancies, respectively. (Figure 26)

Bearing in mind the results obtained, we confirmed that new approaches were needed in our center. Comprehensive healthcare programs carried out by proactive multidisciplinary teams allow us to focus on disease prevention and patient empowerment. (118–120) Moreover, comprehensive medication reviews (35) are needed to identify opportunities to optimize (53–56) patients' drug regimens. Some relevant interventions to reduce medication regimens complexity were summarized for great use of transplant providers in usual clinical practice and detailed in Appendix 5.

Therefore, the HTx population offers an exceptional opportunity to use such innovative holistic approaches to deal with long-term complexity.

7.1.3. LIMITATIONS

This study has some limitations. First, when using the pMRCI score, clinicians should be aware that this index does not include factors such as personal disabilities in the transplant population (e.g. vision impairment, cognitive difficulties, etc.).

Second, this study shows an inevitable selection bias because it included living HTx recipients since a person-to-person interview was needed to obtain essential data. Moreover, we did not include the acute post-HTx stage to allow us to focus on long-term HTx morbidity.

Third, after the performance of this observational single-center study to measure pMRCI-S, interventions in therapeutic regimens were not homogeneous for all the HTx recipients. Therefore, it is not possible to perform an analysis of the impact of pMRCI-S scores on health outcomes over time. Randomized prospective studies designed for this purpose may provide in future a complete study of the impact of the pMRCI on post-HTx outcomes. For now, our estimates of the correlation of clinical variables with the pMRCI-S may be conservative.

7.2. STUDY 2. INTERDISCIPLINARY MOBILE HEALTH MODEL TO IMPROVE THERAPY MANAGEMENT AND CLINICAL CARE AFTER HEART TRANSPLANTATION: AN IMPLEMENTATION STRATEGY STUDY

7.2.1. PRINCIPAL FINDINGS

The steps outlined in this study resulted in the implementation of a holistic eHealth and behavioral-based intervention model in the HTx population in the outpatient setting. Such as other authors, we also experienced that scalable mobile health applications are costly and time-consuming to produce. (129) This is important, since there are several potential barriers when implementing an mHealth program in multimorbid patients which could lead to dead ends in clinical practice. (128,131,185)

Therefore, it is critical for any new development to be based on a depth analysis of feasible solutions to overcome limitations. Consideration of the issues overcome during the implementation of the mHeart may shorten the time period to reach the desired quality standards. Based on the experience gathered, the key points deemed essential in conceiving a new behavioral intervention model are outlined. These recommendations will be used by future developers as a checklist to ensure minimum standards:

- ☑ Before choosing the development company, determine that (i) it is a solvent and solid firm; (ii) its compliance with national standards of quality and safety; (iii) it has previous experience of clinically-tested healthcare systems; (iv) it has favorable opinions of previous developers; and (v) it provides an excellent user help center.
- ☑ Allocate resources to having expert advice on (i) legal, security, and data protection; (ii) medical technology intellectual property; and (iii) medical device regulations and quality evaluation.

- ☑ Assign a provider as a part-time coordinator to facilitate procedures and deadlines, and to liaise with all parties. The recommended skills of the coordinator are a proactive approach, holistic vision, experience of research and innovative projects, ability to work in a team, to have training in a specialty, medication management, behavioral change theories, and patient engagement.
- ☑ First design a general system structure and later adapt it to the target population needs. This will help to ensure end user engagement while compensating the implementation burden and ensuring the scalability of the model.
- ☑ Base the design of the intervention model on already demonstrated major determinants of the efficacy of interventions and patient engagement (i) proactive and trained multidisciplinary teams; (ii) active interaction with end users; (iii) behavioral change theories; and (iv) tailored interventions based on relevant PROMs.
- ☑ Include in the design stage (i) an analysis of end users' expectations, fears and barriers; (ii) expert opinions on the interoperability of the system; (iii) a plan for sustainability and reimbursement according to the interests of the center or health institution.
- ☑ Join forces with patient associations and scientific societies during the design and testing stages to ensure content quality and scalability among centers.
- ☑ Evaluate whether new features that may arise in the testing are (i) incorporated in the prototype (only recommended if they affect the usability and quality of the system); or (ii) addressed in subsequent phases of improvements.
- ☑ Once the final prototype is established, resources should be allocated to provide continuous updates based on users' needs and feedback. This will ensure the system's usability, quality, and persistence over time.

7.2.2. BENEFITS OF THE MHEART MHEALTH STRATEGY IN MULTIMORBID AND POLYPHARMACY POPULATIONS

The information gathered from the opinions of patients and stakeholders allowed us to establish the aims of the mHeart clinical practice improvement model. Thus, the theoretical gains of mHealth described in the literature were translated into real-world strengths and the key software features were designed to achieve them.

First, the **improvement in medication safety and efficacy** achieved the highest agreement by the stakeholders surveyed (88%). Which in line with other authors (162,163,225) is indeed a major determinant in health outcomes. Thus, the main feature of mHeart was to provide pharmaceutical care, with particular emphasis on reducing the impact observed (16,62) of nonadherence to immunosuppressants in the transplant population. To succeed, the mHeart design combined multilevel strategies inspired on previous successful experiences, (138,226,227) including educational, motivational and tailored Internet behavioral-based interventions to be delivered by a proactive team. (72,78,133)

The 2 following greatest strengths of the mHealth approach were **improving continuity of care and information flow** (81%) and **solving patient and caregiver queries** (77%). Indeed, based on the opinions of patient association representatives and in line with the findings of other authors, (126,162) chronic patients are seeking more communication opportunities and better coordination among health providers.

In this sense, mHealth programs represents a unique opportunity to combine human support and new digital skills to reach a therapeutic alliance with the patient. (160,228) Software functions to promote patient-professional interaction (154,159) are therefore essential in a patient-centered model targeting the outpatient population such as mHeart.

Other relevant gains of mHealth reported by stakeholders were **enhancing patient's self-management** (77%), **early detection of symptoms or adverse effects** (65%), and **the use of patient-reported outcomes to allow preventive strategies** (65%). Indeed, the current scenario, in which patients are demanding co-responsibility, (75) provides a strong opportunity to engage patients in electronically recorded patient-reported outcomes.

In addition, mHealth is an oportunity to train patients in how to detect alarm symptoms and how to act when they arise. Indeed, the use of patient-reported outcomes has previously shown impact on medication efficacy and safety, (128) patients' quality of life, and even survival. (132)

Tehrefore, it is expected that preventive Internet-based interventions based on patient-reported outcomes will be determinant to improve health outcomes in outpatient care in the near future.

7.2.3. BARRIERS AND FACILITATORS TO IMPLEMENTING THE MHEART MHEALTH APPROACH

The first potential barrier to implementing an mHealth solution according to 58% of stakeholders' opinions was the **increase in clinician's workload**. However, in line with previous studies, (128,141,229) the burden experienced during the mHeart implementation was mainly derived from several other reasons such as achieving a well-designed theory-based framework of the intervention model, ensuring legal and security requirements, involving the healthcare team in training and workflow, and, ultimately, several organizational barriers.

These tasks were highly demanding of time and therefore it is strongly recommended that future developers perform an initial roadmap based on successful previous experiences. Moreover, an initial agreement with all the parties involved on the stages and their responsibilities is also critical to reduce burden.

The second most widely agreed barrier, by 50% of respondents, was **lack of interoperability**, which has also been identified by other authors (126,131,185) as a major risk factor for unsuccessful eHealth approaches becoming isolated from the health care system. This challenge was technically demanding but entails improvements in safety and quality. Indeed, mHeart testing of interoperability revealed that transcription errors may be avoided, the time spent typing patient data decreased, and a better coordination among health providers may be achieved.

Other well established major barriers of eHealth strategies in clinical practice, (180) and in line with respondents opinions, were the **lack of models for funding** (15%) and **reimbursement for mHealth services by health systems** (54%). Although local guidance is fortunately growing, (131,230) there is a delay in the implementation of new telemedicine laws. (231) This causes uncertainty about minimum quality standards and hinders scalability because of a lack of reimbursement models. (138,181,232) The initial mHeart funding was based on grants and has been detailed in the online Mendeley dataset to increase transparency and inspire new developers to overcome this barrier. (1)

The risk of **patient's resistance to using technology or the digital divide** was also a potential barrier according to 23% of stakeholders, and is in agreement with previous finding in multimorbid patients. (126)

Nevertheless, almost all of recipients in this study owned a cellphone and agreed on the utility of mHealth approaches such as mHeart. Thus, these data reinforce the idea of access, widespread use and acceptance of technology in the HTx population, such as previously observed in transplant recipients. (190,233) Nevertheless, high levels of attrition are a real issue in eHealth programs. (159) Thus, a persuasive design focused on enhancing user adherence is highly recommended. (154,160,228) Moreover, patients' opinions should also be carefully considered, with special emphasis on identifying potential barriers. In the mHeart interviews, as many as 47% of recipients were interested in using a complementary website and 22%

reported the need for a tutor to use the tool. Consequently, a patient profile website was provided, and a help center was hired to provide human assistance and initial training to users. According to other authors, (159) this latest strategy has potential to increase user engagement without increasing provider burden.

7.2.4. OPPORTUNITIES DERIVED FROM THE MHEART MODEL

It is important to note that the implementation of behavioral change technology models targeting complex populations such as mHeart demands a multidisciplinary approach. After the design of the mHeart system, several time-consuming issues remained to be solved, such as interoperability, implementation, security, and quality. Moreover, the involvement of the interdisciplinary team, patients, and several experts was essential for the success of the platform, but also required complex interactions.

Finally, operating this process is a highly demanding task, requiring a coordinator profile with certain skills. The leadership of the mHeart implementation by the Pharmacy Department provided a strong opportunity to expand the role of clinical pharmacy into the teams, while making this provider visible to patients, families, and institutions. Likewise, eHealth is a valuable opportunity to expand the benefits of pharmaceutical patient counseling and therapeutic drug monitoring in health care systems. (137,234)

7.2.5. LIMITATIONS

This study has some limitations to note. The study did not address the efficacy and sustainability of the mHeart approach over time, since it focused on the model implementation and scalability phases.

Primarily, the feasibility of a hypothetical clinical intervention based on the mHeart system should be properly assessed before been scaled to larger research. Moreover, based on ISRII recommendations, (129) the validity of

the electronic versions of the questionnaires used to measure diverse health domains in the mHeart system should be also evaluated.

Future clinical applications of *the mHeart strategy* will provide its impact on health outcomes. In future research conducted with this model, and depending on the desired behavior change, details should be provided on when and under what conditions interventions will be delivered. (169)

7.3. STUDY 3. THE MHEART MOBILE APP TO DETECT MEDICATION NONADHERENCE IN THE HEART TRANSPLANT POPULATION: VALIDATION STUDY

7.3.1. PRINCIPAL FINDINGS

This article was focused on improving screening opportunities for medication adherence since MNA to immunosuppressive treatment is a direct cause of graft loss and death in the HTx population. The mHeart system uses electronic questionnaires (i.e. the ePROMs) to identify nonadherent recipients and help to increase the feasibility of self-reporting overcoming current in-clinic limitations. (129,140)

Moreover, these ePROMs are also used to provide valuable information to health providers to implement early and personalized interventions through mHealth. Indeed, eHealth interventions show a promising impact on prompting changes in health behaviors such as medication adherence. (127,136,141,147,148)

However, according to the Directions for the International Society for Research on Internet Interventions (ISRII), (129) a prerequisite before recommending its widespread use for Internet delivery is to demonstrate the accuracy of ePROM scores and their relationship with traditional in-clinic methods. (151)

Given this background, the main challenge of this study was to validate mHeart to measure MNA in acute-stage HTx recipients by assessing the psychometric properties of ePROMs compared with the paper form. But also, secondary challenges were to obtain greater patient satisfaction with the mHeart tool and to explore the impact of a multilevel theory-based eHealth treatment (*the mHeart strategy*) on MNA rates in order to scale the program to larger research.

Because the mHeart ePROMs showed to have met the minimum standards set by the ISOQOL, (84) they can be used in patient-centered outcomes research and widespread clinical practice. The electronic self-reporting method implemented in the mHeart® medical device showed to be as effective as the on-site traditional approach to remotely identify MNA in the HTx population.

Moreover, ePROMs showed the potential to overcome previous limitations with traditional on-site methods. The electronic approach required fewer in-clinic facilities and a reduced time required to record ePROM responses in patients' medical records. These advantages reduced burden and enabled the pharmacists to focus on clinical tasks. This is clinically significant as pharmacist intervention is associated with a better use of evidence-based therapies, reducing medication errors and emergency department visits while increasing patient satisfaction. (99)

Alarmingly, 42% of early-stage HTx recipients included in this study were unaware of the consequences of MNA and 39% were nonadherent to immunosuppressive treatment. Polypharmacy was common in these patients taking a mean of 13 (SD4) different drugs per day without including over-the-counter drugs. The theory-based multifaceted intervention program produced an encouraging improvement on co-medication MNA between 16% and 26% [*P*-value<.05] in early post-transplant recipients within whom MNA is a high-risk behavior with a huge impact on survival. (62)

In the case of immunosuppressive treatment, adherence rates have also significantly improved in a third of the recipients. This figure is higher than those reported by most studies and this is considered highly effective when improvement was >20%. (73) Therefore, since the improvement in MNA in our exploratory study was higher (30%), the strategies applied proved to be synergistic and to enhance the effectiveness of the program. (86–88)

7.3.2. CLINICAL IMPLICATIONS

Equally important, excellent patient satisfaction and usability scores were also observed. Patients adhered well to the study protocol and provided excellent feedback. Overall patient satisfaction with the mHeart approach was 9 (SD2) and all patients surveyed reported they would recommend the mHeart platform to other HTx recipients. Among the benefits of the mHeart approach, patients highlighted personalized communication, support from professionals, and self-empowerment, which were the most relevant criteria used to design the mHeart intervention. These results reinforced the transplant team ambition to implement and scale the healthcare program.

Since the study was not powered to demonstrate intervention effect, our preliminary results required confirmation in a larger clinical assay established thereafter. Because little is known about how to successfully translate effective adherence-improving interventions into clinical practice, the EMERGE standards (70), the TCS (88) and the CONSORT-EHEALTH reporting criteria (153) standards were followed to support the scale-up of the intervention methodology used.

In conclusion, electronic self-reporting assessments provide a highly sensitive MNA measure in the transplant population to complement traditional more time-consuming methods, such as blood assays or medication refills. (64,71) Moreover, the mHeart program showed great promise in guiding professionals' interventions with the potential to optimize HTx health outcomes. The feasibility and effectiveness found in this study are a promising starting point that encourage following this path to curb the widespread problem of MNA.

7.3.3. LIMITATIONS

There is some potential limitations in this study. First, our study includes a limited but representative 86% of all early-stage HTx recipients in our center. This characteristic is common in the transplant population, since the prevalence is limited. (77) We did not enroll chronic-stage recipients for the following reasons: (i) early post-transplant MNA is a high-risk behavior with a huge impact on survival; (62) (ii) we wanted to avoid wide heterogenicity in chronic-stage providers and treatments; (iii) we wanted to avoid chronic-stage recipients having to travel to the clinic for the study; and (iv) we wanted to avoid to interfere in a hypothetical future RCT in chronic-stage patients. In addition, although early-stage recipients are typically better adherers, (28,235) this did not prevent us from observing an effect in the highest-risk period after transplant.

Second, the interval between MNA assessments may have led to recall bias. Although this bias could have influenced the electronic score, this limitation is intrinsically related to the validation methodology. The electronic and traditional methods were assessed the same day to ensure they are performed in similar conditions and in patients with similar psychological and functional status.

Furthermore, the short study periods used were methodologically grounded according to the main study aim of validating the ePROMs. In *sensitivity to change measures*, a 1-month interval is considered adequate to measure the validity of an indirect smartphone health measure. (204,205) Moreover, fortnightly assessments are sufficient to identify additional MNA in the transplant population. (71) In *reproducibility measures*, intervals of 1-2 weeks are common. (236) Therefore, a 7-day interval was selected to minimize the effect of possible confounding variables (210) related to the multifaceted factors affecting post-Tx MNA. (71,79)

7.4. STUDY 4. IMPROVING PATIENTS' EXPERIENCE AND MEDICATION ADHERENCE AFTER HEART TRANSPLANT USING A MULTILEVEL MHEALTH INTERVENTION: THE MHEART RANDOMIZED CLINICAL TRIAL

7.4.1. PRINCIPAL FINDINGS

Before the intervention, the percentage of HTx recipients nonadherent to immunosuppressive treatment was worrisome according to the SMAQ questionnaire (64%) and higher than observed in another series (15-50%). (17,64,78,237) This figure confirmed the urgent need for an innovative strategy to deal with this problem in a well-established HTx outpatient setting.

The new intervention established required support by the mHeart software without increasing the HTx in-clinic burden. This tool was an already designed and validated mobile health app for conducting comprehensive follow-up according to recipients' needs. The greatest value of the mHeart system was to enable health providers to perform intensive digital individually-tailored behavior change interventions in order to empower patients in medication self-management. Therefore, the mHeart technology was used as a modern way to increase the opportunity for provider-recipient interactions in a currently digitalized society.

The results of this study indicate that *the mHeart strategy* has been highly effective in improving MNA rates. Indeed, medication adherence was 65% higher in the intervention group at the end of the study (T_2). This figure is certainly higher than those reported by most studies using traditional educational interventions, (73,79) but is also higher than in-clinic multilevel theory-based interventions considered highly effective when improvement was >20%. (73)

In contrast to other studies, our program is the first designed to combine high-quality strategies (78,86,87) such as deliver multilevel personalized professional-patient interactions through an mHealth platform in adult HTx

recipients and using a behavioral framework. Indeed, human support and tailored interventions have been shown to be a requisite to improve MNA rates throughout eHealth. (79,127) In addition, our intervention meets 70% of the TCS criteria, indicating that the study design complies with the theoretical basis of the intervention (88) and is correlated with the effectivity of the behavioral change interventions implemented. (96) Therefore, as many authors have hypothesized, (86–88) we proved that multilevel behavior-based eHealth strategies are synergistic and enhance the effectiveness of an intervention to improve medication adherence.

Another relevant point based on the results of this study is that, in line with our previous experience, (214) any therapy management program must include optimization techniques to reduce therapeutic complexity in populations with polypharmacy such as HTx recipients. Indeed, since most of the therapeutic complexity observed in our population was derived from *drugs to treat comorbidities* in our HTx population, (213) the number of these additional therapies and over-the-counter medication was addressed and significantly optimized at T_2. This figure, and in line with those of other authors, (40–42) may also be correlated with the improvement in medication adherence rates in our study.

Because of the multilevel factors affecting MNA in the transplant population, (16) we needed not only to reduce therapeutic complexity but also to improve patient experience. By looking at various aspects of this patient experience in the domains of medication management, we assess the extent to which patients perceived care that was responsive to individual patient preferences, needs and values. Indeed, it was enlightening to discover that 2 patients who received the exact same care, but who had different expectations of how that care should be delivered, could reach different conclusions and statements about medication because of their distinct expectations.

Measuring patient experience showed the weaknesses in medication beliefs and guided the eHealth interventions to convert them into strengths (238) in a more self-reliant and co-responsible recipient. Important aspects

addressed were easy access to information on regimens, good communication with healthcare providers, a reduced appointment burden, and better coordination among healthcare processes. (239) Indeed, RCT have provided solid evidence that humanizing healthcare also improves clinical outcomes. (240) Thus, the improvement observed at the end of the study in patient-experience variables may also enhance medication adherence rates.

7.4.2. FUTURE IMPLICATIONS

According to the ISRII experts, the applicability of eHealth study results in different contexts is highly valued. (129) Therefore, based on the positive results obtained, we aim to adapt *the mHeart strategy* to other multimorbid and therapeutically complex populations in our Hospital outpatient clinics. With the aim of extending the research study into clinical practice, we included an in-depth description of the design of the intervention model according to the ISRII (129) and the CONSORT-EHEALTH reporting guidelines. (153) This contains an in-depth description of the behavioral change model applied in this study (Appendix 2 and 3), providing a better understanding of the causes of patients' behavior and how the intervention works, (89) thereby increasing treatment effectivity, comparability, and scalability. (129,153)

Another important issue is the absence of patients who voluntary dropped out after randomization in the RCT intervention group. Attrition rates often compromise the scalability of eHealth research into clinical practice. (153) This lack of attrition may be influenced by the in-depth experience gained during the previous feasibility study (*Study 3*). (214) Likewise, it may be correlated with the use of personalized behavioral content in the interventions, since it has been shown to decreases dropouts in RCT. (177) These positive results indicate the adequate feasibility of *the mHeart strategy* intervention workflow and encourage the generalizability of the strategy performed.

Furthermore, the generalizability of *the mHeart strategy* also involved evaluating the level of human involvement required for routine application outside a RCT setting. (153) This point was properly assessed in *the mHeart*

strategy validation study, showing a low professional burden related with the intervention (*Study 3*). (214)

Another important finding was the marked reduction in the patients' need to travel to in-clinic appointments at the end of the study in the intervention group. Therefore, based on the results obtained, a long-term mobile-based approach will be continued through the mHeart platform in more than a half of the HTx in our Hospital outpatient clinic. These recipients would, therefore, periodically receive person-centered feedback by health providers in order to maintain the improved medication adherence achieved.

In conclusion, the implementation of behavioral change technology models targeting complex populations in our setting demands human involvement in an interdisciplinary environment with a lower patient and professional in-clinic burden. Moreover, multilevel interventions such as mHeart require that the team should be properly trained in digital behavioral skills to deliver eHealth interventions. (72,73,90,241)

7.4.3. LIMITATIONS

This study has some limitations. First, state-of-the-art measures such as self-reporting could under-represent MNA, as reported in previous studies. (63,71,85) Nevertheless, since there is no gold standard in MNA measurement in the transplant population, (63) we combined several quantitative and qualitative adherence tools aiming to capture a wide variety of patients. The high cost of electronic monitoring and its impact on improving adherence (since it is a monitoring device used by the patient at home), were considered limitations for its applicability in this study.

The methods were selected because of their generalizability to larger populations, including their simplicity of use and scoring. With this aim in mind, we used a blood test assay as an objective method and self-reporting as a subjective method. Selecting the optimal self-reporting instrument was crucial since it is critical to use validated questionnaires with good psycho-

metric properties such as the SMAQ or BAASIS questionnaires. In addition, a composite adherence score (i.e. patient self-report, CV assay results, and missed visits) was used because it has proven its validity for "screening" (i.e. first step) rather than diagnosis because of its high sensitivity. (80)

Second, participant selection bias may have occurred because nonadherent recipients in the intervention group may have been more likely not to use the mHeart platform or to decline to be included in the study. However, solely as many as 36% recipients not using the mHeart software every day at the end of the study were nonadherent according to the SMAQ, and solely 3% of patients declined to participate.

Third, as usually occurs in web-based trials, (153) it was not possible to blind the participants or the provider administering co-interventions for budgetary reasons. Subjective preferences were unlikely to mask baseline results since diverse solutions were implemented to mitigate subjective interpretations. Chronic-stage recipients had no previous interventions by the pharmacist prior to the baseline visit, and baseline measures were obtained before the allocation was known. Furthermore, face-to-face visits used a fixed template, which was recorded in the patients' electronic health records immediately after the end of the face-to-face visit. A retrospective review of these records by 2 research assistants, neither of whom belonged to the therapeutic team, and an independent statistician was also implemented to mitigate subjective interpretations.

Fourth, the results of the blood assay method should be interpreted with caution because 3 months after the start of the study the *immunoassay* technique was changed for a more sensitive technique, the *liquid chromatography tandem mass spectrometry*. As a consequence of this, physicians may have increased immunosuppression treatment doses in order to reach therapeutic ranges. Therefore, a significant improvement in variability in the assay assessment in this study may be masked. Besides that, a tendency of reduction of overall variability in blood levels was found and supratherapeutic levels were significantly improved.

IMPLICATIONS OF THE THESIS AND CURRENT STATUS IN CLINICAL PRACTICE

8. IMPLICATIONS OF THE THESIS AND CURRENT STATUS IN CLINICAL PRACTICE

Innovative research projects on health institutions are typically short-lived practices with a lack of scalability to usual care. This transition was, however, a priority for *The mHeart Study*, based on prior demonstration of enhanced results. With this aim in mind, after the clinical testing finished in 2018, the mHeart system was temporally suspended to improve security and functional components. After these adjustments, the mHeart model was extended into clinical practice in January 2019. Nevertheless, the transition from an innovation project to an established practice was particularly challenging: this entailed funding and organization adjustments led by the Pharmacy Department and the Heart Transplant Unit and also required input from patients, interdisciplinary health professionals and the institution managers.

PHARMACY DEPARTMENT IMPLICATIONS OF *THE MHEART STUDY*

The implementation of *The mHeart Study* research project in the Hospital de la Santa Creu i Sant Pau and its scalability to usual clinical care was challenging and extremely time consuming for the Pharmacy Department. The mHeart model was coordinated by a clinical pharmacist and directed by the head of the Pharmacy Department. The pharmacist coordinator worked part-time every day for 2 years to implement the new healthcare model and build up the system. Additionally, the senior pharmacist with managerial experience was also essential to achieve the institutional structure needed to implement and scale the project. The setting-up period was followed by 2 more highly demanding years to continue with the pilot project and subsequently clinical testing to improve medication adherence. Therefore, the project was especially challenging in a European context where hospital pharmacists provide pharmaceutical care to a large number of patients, given the small number of full-time clinical pharmacists compared with hospitals in the United States. (115)

Innovative practices require the participation of experts from multiple fields. Nevertheless, the mHeart model was the first mHealth project implemented in the Institution and consequently the necessary structure was created from scratch. For instance, institutional support was essential, meaning that agreement had to be obtained from the Hospital department managers to allocate professionals' time to work on the project. Additionally, burden was associated with achieving coordination among these Hospital departments to create the institutional structure to support eHealth programs. A well-established structure has now been achieved, involving professionals from different departments such as the Legal Department, the staff in charge of patient data protection and confidentiality, the Information Systems Department and the Innovation Research Institute. Even these tasks were highly demanding for the Pharmacy Department, the effort was worthwhile because future mHealth implementations will be facilitated by an already established structure.

In addition, it was essential that the project was recognized by the Institution as usual practice and was included in routine workflow. In this sense, dissemination of the results obtained from the implementation of the model, pilot project, and clinical testing helped to make the value of *The mHeart Study* known. For instance, the preliminary results of the project have been orally presented by the coordinating pharmacist at scientific meetings, not only pharmacy meetings but most of them transplant or cardiology related. Likewise, many abstracts were sent to national and international congresses. Additionally, the model and its results have been reflected in this thesis work and in future manuscripts on additional health outcomes of the clinical testing.

In our experience, the use of eHealth tools by the clinical pharmacist led to a change in the current model of providing pharmaceutical care in therapeutically complex outpatient populations in our Hospital. This new model implied a shift from sporadic interaction with patients during on-site visits, to a continuous telematic follow-up by the provider. Moreover, the eHealth model requires patients to be proactive and co-responsible in their therapy

management. As well, innovative tools demand proactive health providers far from the paternalistic role used in the past.

Based in the mHeart clinical testing, telematic care enhanced clinical pharmacist-patient interaction and, certainly, the number of relevant pharmaceutical-care interventions solved per day. Therefore, telepharmacy went beyond the research project and was implemented in the HTx outpatient usual clinical practice. These tailored interventions are related to responses to patient consultations through the platform such as treatment queries (e.g. potential harmful drug-drug interactions, doubts about the immunosuppressive schedule) or are related to symptoms and medication adverse effects (e.g. fever, diarrhea, vomiting, fever, etc.). Likewise, the eHealth interventions were also derived from proactive involvement of the pharmacist in managing decompensated biomeasures, such as blood pressure or glycaemia, according to patient-reported data. Thus, real-life data aimed to facilitate the optimization of therapeutic regimens together with physicians in the at-home setting. Furthermore, the responses of the patients to electronic questionnaires guided the clinical pharmacist to detect patients requiring special attention, for instance because medication nonadherence.

RELEVANT STEPS OVERCOME AFTER THE END OF *THE MHEART STUDY* RESEARCH PROJECT

Once the institutional structure to implement the mHeart model was built and the clinical testing phase was finished in February 2018, the pharmacist coordinator's time on mHeart practices was invested in the next important steps.

The first step needed was to improve the security, functionality and usability of the mHeart system. These improvements were based on the experience acquired during the clinical testing period including the opinions of experts, professionals, and patients. These tasks required temporarily suspending the mHeart system from June 2018 to January 2019 to allow the improvements to be implemented by the technical team. Currently, the platform has been used by more than 100 HTx recipients and this rate is expected to

rise to 200 patients in 2020. However, technological improvements or new features will always be necessary, which will require assistance from the technical team and a scientific coordinator throughout the lifetime of the system.

The second important step was to achieve an integral and interdisciplinary follow-up of patients through the mHeart system. Relevant life-style outcomes such as insomnia, anxiety, depression, diet or exercise, were not properly addressed during the study because demands an interdisciplinary HTx team using the mHeart system comprehensively. With the cooperation of the HTx cardiologists, although the primary aim prompting *The mHeart Study* was to provide support to HTx recipients nonadherent to medication, this goal was not be isolated from other relevant health outcomes. With this aim in mind, from the very beginning, the rest of the clinical team were involved in the mHeart system design as detailed in *Study 2*. Therefore, the mHeart mobile application developed aimed to provide an integral and interdisciplinary follow-up in the transplant population.

During the research phase of *The mHeart Study*, the clinical pharmacist acted as a link among patients and physicians as a case-manager. Meanwhile, HTx team providers carried out traditional in-clinic follow-up. According to physicians' feedback reported in *Study 2*, the main barrier to their direct involvement in mHeart follow-up was the workflow burden related to telematic care. Nevertheless, *Study 2* and *Study 3* have demonstrated that this potential limitation to eHealth implementation became less relevant once the mHeart workflow became established. Therefore, at the end of the clinical trial and taking into consideration the directions of the physicians, the mHeart healthcare intervention was redefined to include amendments to the clinical tasks of the majority of the members of the HTx team.

Currently, many health providers are interacting directly with the patient by using the mHeart system (i.e. including 1 psychologist, 2 nutritionists, 1 social worker, 2 rehabilitation physicians and the clinical pharmacist). The involvement of these interdisciplinary providers in the mHeart healthcare

model releases the clinical pharmacist from her case-manager duties, thus, allowing this professional to focus on working with patients, families and the HTx team to provide a comprehensive management of the therapy. This is important because in *Study 1*, HTx recipients showed the highest levels of therapeutic complexity compared with other chronic populations, and because, according to the international HTx guidelines, inclusion of a pharmacist in the transplant team is a quality criterion.

The third step to be overcome after scalability of *The mHeart Study* was the simplification of the research project practices. The tasks implemented during clinical testing often cannot be sustained in usual care because they are time consuming. Clinical testing of mHeart required a full-time clinical pharmacist. The tasks performed encompassed providing pharmaceutical care to outpatient HTx recipients, including visits and mHeart system follow-up, as well as case-manager duties and system coordination with the technical team. This full-time model of the clinical pharmacist, which has been implemented in other countries such as the United States, is not affordable in our context. Therefore, to ensure the sustainability of the program, the most valuable practices were selected, prioritized and structured in clinical protocols. This facilitated the involvement of other pharmacists in the mHeart healthcare model and prevented the program from depending solely on the pharmacist coordinator.

The fourth important step performed by the head of the Pharmacy Department and the pharmacist coordinator was to work on the mHeart funding and reimbursement model. This point is crucial to keep the research project alive and also to achieve the generalizability of mHeart to usual care. The delay on reimbursement laws by health authorities difficulted the practice implementation. Nevertheless, the clinical activity performed through the mHeart system has been counted by an annual assessment of ambulatory telematic pharmaceutical care interventions (i.e. relevant interactions performed via video call or message).

Furthermore, the cost of the technical maintenance of the platform must be met once the funding of the project has finished, which involves technical support to end-users and also technical improvements. This cost had previously been financed by the Pharmacy and Cardiology Department, and is going to be funded by a contribution from the pharmaceutical industry to the Institution for the next 4 years. In conclusion, reimbursement depends on the implementation of new telemedicine laws by health authorities and the funding model needs to be continuously re-evaluated with the Institution's managers to prevent discontinuation of the mHeart service.

The fifth critical step in the mHeart model was to continue working on the interoperability between electronic health records and the mHealthCare System. Since the 2 systems are currently connected and there is 2-way data sharing, the next goal in interoperability will be to upload electronic medical prescriptions into the mHeart system. This would allow pharmacists to avoid the risks and burden associated with the transcription of the prescription and focus on ensuring the therapy adequacy.

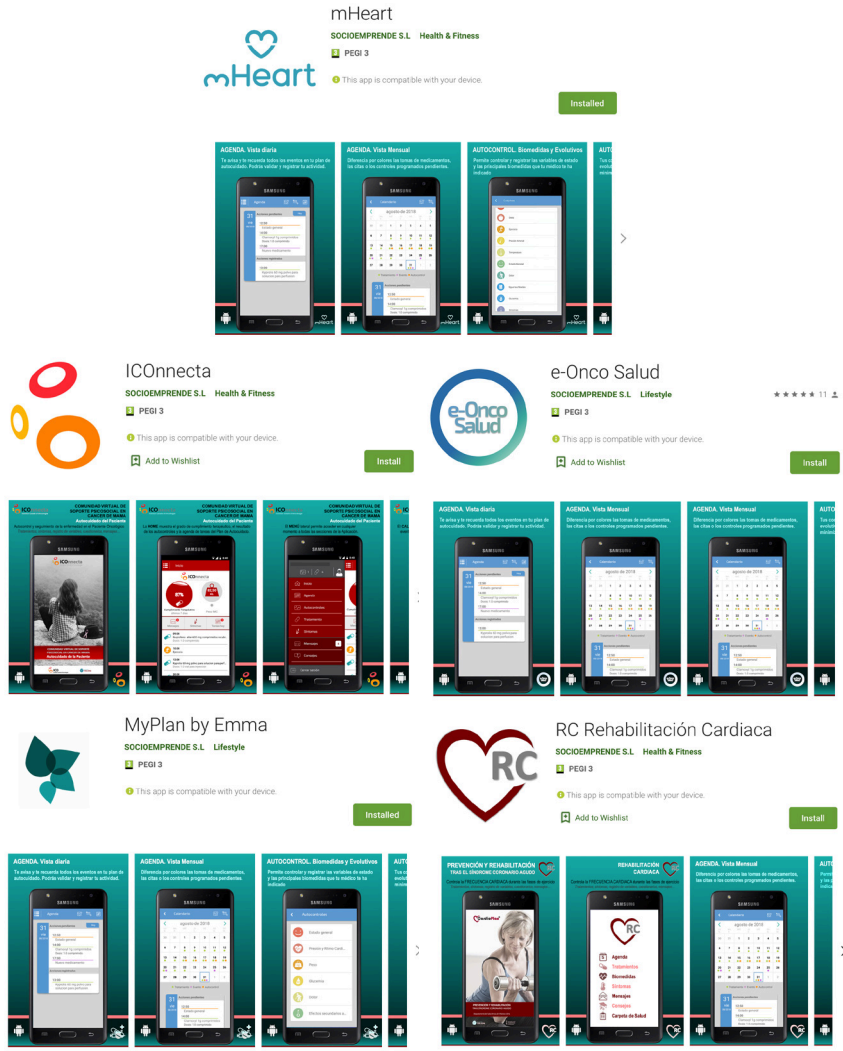
Additionally, other possible improvements on mHeart interoperability will be to connect the Hospital's appointments system to the mHeart agenda, or even to connect mHeart with the primary care system. These new features will result on a great improvement on mHeart usability.

Finally, an extremely challenging step is to adapt the mHeart model to other complex chronic populations in the ambulatory setting of our Hospital. Indeed, according to the ISRII experts, there is strong demand for public dissemination of eHealth programs in different contexts. (129) Therefore, adapting the structure of the mHeart system to the needs of other populations would help to recoup the initial cost and implementation burden.

Likewise, other institutions will benefit from an already established and clinically tested software as a starting point to avoid the burden of developing

such a system from scratch. An example is how the structure of the mHealthCare System, designed as the basis to develop mHeart, has been scaled to different populations by other healthcare centers (i.e. MedPlan+, e-Onco-Salud, ePrematur, Entrena EII, Gerar, RC Rehabilitación Cardiaca, ICOnnecta, among others).

Figure 30: A common eHealth environment. The mHealthCare System, designed as the basis to develop mHeart, has been adapted to different populations by Spanish healthcare centers.



FUTURE CLINICAL LINES EMERGING FROM THE THESIS

9. FUTURE CLINICAL LINES EMERGING FROM THE THESIS

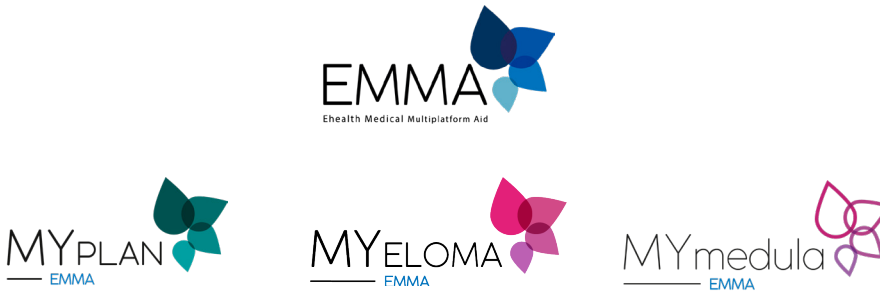
eHealth programs directed to complex populations in the ambulatory setting are becoming an established line of work for the Pharmacy Department of the Hospital de la Santa Creu i Sant Pau. There are many factors that encourage the coordinator and the head of department to invest in this innovative line. For instance, telematic ambulatory care increases the number of therapeutically complex patients who benefit from pharmaceutical care. Moreover, human relations among patients, families and health providers may be enhanced with the aim of improving patient satisfaction and involvement in the health system. Additionally, interdisciplinary eHealth projects lead to increased interaction among clinical pharmacists and other health providers, expanding pharmaceutical care in healthcare systems. Finally, such as in many other areas of modern society, the future of healthcare lies in technology. Thus, following in this line, the Institution may be a model for the implementation of integral eHealth programs in ambulatory care clinical practice in the near future.

With these opportunities in mind, new projects are in progress based on the mHealthCare System (the basis of the structure of the mHeart system). Because eHealth had been demonstrated to be successful when directed to the specific characteristics of a population, (141,242) each new project was individually evaluated to decide which sub-product of the platform was most appropriate to the new clinical specifications. However, the potential functionalities of the new version were simplified to the essential changes. Moreover, currently there is vast literature on eHealth design and quality developments. Consequently, the new versions incorporated the standards reported in the literature to ensure the validity of the new systems.

Currently, an Onco-Hematological platform has been created in collaboration with other Spanish hospitals based on the mHealthCare System. The new system has been designed as a single platform with several profiles depending on the clinical specifications of each health condition. At pre-

sent, the profiles already designed are multiple myeloma and bone marrow transplant conditions. With this aim, innovative technology components have been designed on an interdisciplinary basis with the aim of implementing comprehensive clinical management in these complex populations. Currently, the development stage of the new technology is on-going coordinated by the thesis author and assisted by many other health providers.

At the same time, there are some other mHealth projects in progress, some of them based on the mHealthCare System sub-product, MedPlan+. (243,244) This platform was created on the basis of mHeart by the Pharmacy Department of the Hospital Clínic (Barcelona, Spain) to track medication adherence in the chronic elderly population. Currently, a new version of MedPlan+ has been named MyPlan by EMMA (EMMA i.e. eHealth Medical self-Management Aid), which has been adapted to perform an interdisciplinary follow-up of any multimorbid population with polypharmacy. Thus, the new platform is a generic system that can be used in any multimorbid patients by activating or omitting certain modules (e.g. glycemia module or blood pressure module) that define the target patients' specific comorbidities.



The new MyPlan will be clinically tested in diverse multilevel projects coordinated by the Pharmacy Department. For instance, one of them will be a single-center study carried out in the emergency department and focused on secondary prevention of medication-related problems. Likewise, a promising multicenter national study to evaluate the impact of the system on

dyslipidemia management in secondary prevention patients after a coronary syndrome will be also performed. In addition, other Spanish centers are implementing MyPlan in their Institutions assisted by the experience gathered during this thesis study.

In conclusion, eHealth programs are constantly evolving including dynamic models with huge potential in the near future. To continue growing and creating evidence on the use of the eHealth in our setting, many future adaptations of the current mHeart model will be necessary. These new eHealth projects coordinated by the thesis author will have common relevant clinical aims such as improving clinical practice workflows, safety and efficacy of the therapies, patient-provider interactions and patient empowerment.

The success and scalability of these innovative projects in our center will depend on health providers engagement with eHealth, new interoperability solutions, adequate institutional support, and government reimbursement models. Therefore, the implications of *The mHeart Study* thesis research and the eHealth model established will be a promising starting point for an already emerging way of providing further assistance to the most complex populations based on eHealth by the Health Systems.

CONCLUSIONS

10. CONCLUSIONS

10.1. STUDIES' CONCLUSIONS

STUDY 1

Multimorbidity and medication complexity: New challenges in heart transplantation

- Multimorbidity in chronic-stage HTx was alarmingly high, with an average of 6 chronic comorbidities, treated with lifetime use of 12 different drugs per day. Therapeutic complexity, measured as the *total pMRCI-S score*, was higher than that reported in previous studies in chronic diseases. Multivariate analysis showed that this finding was mainly due to a higher number of *drugs to treat comorbidities*.

- The pMRCI score was found to be a sensitive method allowing identification of the factors determining therapeutic complexity after HTx, including dosage form, dosing frequency, additional instructions and medication categories. This could help health providers to select strategies to reduce pMRCI-S values.

STUDY 2

Interdisciplinary mobile health model to improve therapy management and clinical care after heart transplantation: An implementation strategy study

- A holistic mHealth-based interventional model to improve medication management and clinical care in multimorbid populations with polypharmacy was successfully developed and implemented in the HTx population in the ambulatory setting. Digital behavior change interventions performed by an interdisciplinary team were designed to promote behavior change among patients. Relevant factors that had to be overcome for the model to succeed were ensuring data confidentiality and the system's interoperability, as well as mitigating end users' digital divide and workload.

- Patients and professionals expressed their agreement on the potential benefits of an mHealth approach in highly complex populations such as HTx recipients in our setting: to improve therapy management, patient empowerment, and patient-provider interactions. A total of 98% of the patients confirmed that they were willing to use the mHeart system.

STUDY 3

The mHeart mobile app to detect medication nonadherence in the heart transplant population: Validation study

- The mHeart electronic questionnaires (ePROMs) to measure medication adherence met the validation standards and proved to be as effective as the traditional on-site method in identifying nonadherent recipients (*Phi*>0.7). This finding supports the widespread use of the mHeart ePROMs in larger research and clinical practice.

- The exploratory study showed that the multilevel behavioral change intervention established, *the mHeart strategy*, was highly effective since the improvement in adherence to immunosuppressive medication was 30%.

- The electronic mHeart approach demonstrated its potential to overcome the limitations of traditional on-site methods to manage medication adherence by eliminating potential professional interpretation of ambiguous responses, requiring fewer in-clinic facilities and reducing the time required to record responses in patients' medical records, since the systems have been integrated.

- Patients adhered well to the study protocol and provided excellent feedback; overall satisfaction with the mHeart approach was 9 (score 0-10) and 100% of the patients would recommend it to other recipients. Patients highlighted personalized communication, support from professionals, and self-empowerment as the most important benefits of the mHeart interventional program.

STUDY 4

Improving patients' experience and medication adherence after heart transplant using a multilevel mHealth intervention: The mHeart randomized clinical trial

- An alarming 36% of the HTx outpatient population were nonadherent to immunosuppressive treatment at baseline according to the SMAQ test, and 41% of patients were unaware of the consequences of forgetting to take their antirejection medicines. These rates confirmed the urgent need for strategies to deal with this problem.

- *The mHeart strategy* positively impacted on the health outcomes preestablished. At the end of the study, medication adherence rates were statistically significantly improved in the intervention group (85%) versus the control group (46%). Confirming that the multilevel behavior-based eHealth interventions used enhance the effectiveness of a strategy to improve medication adherence.

- *The mHeart strategy* had a positive impact on patients' experience of therapeutic regimens. The degree of patient-perceived inconvenience and patients' knowledge of their therapeutic regimens showed a statistically significant improvement in the intervention group versus the control group.

- *The mHeart strategy* showed statistically significant reductions in the number of patients needing to travel to the clinic for follow-up appointments (65%) versus the control group (35%). The mHealth approach will be a feasible way to continue providing long-term advanced individually-tailored interventions by health providers to HTx recipients in the at-home setting.

10.2. GENERAL CONCLUSIONS

- Multimorbidity in chronic-stage HTx was alarmingly high. Therapeutic complexity, measured as the *total pMRCI-S score*, was higher than that reported in previous studies in chronic diseases and this finding was mainly due to a higher number of *drugs to treat comorbidities*. The pMRCI score was found to be a sensitive method allowing identification of the factors determining therapeutic complexity after HTx. This tool could help health providers to select strategies to reduce therapeutic complexity.

- A holistic mHealth-based interventional model to improve medication management and clinical care in multimorbid populations with polypharmacy was successfully developed and implemented in the HTx population in the ambulatory setting. The potential benefits of this model in our setting according to stakeholders' opinions were to improve therapy management, patient empowerment, and patient-provider interactions. Moreover, a total of 98% of the patients confirmed that they were willing to use the mHeart system.

- The validation study showed that the mHeart electronic questionnaires (ePROMs) to measure medication adherence met the quality standards. The exploratory study showed that the multilevel behavioral change intervention established, *the mHeart strategy*, was highly effective since the improvement in adherence to immunosuppressive medication was 30%. Moreover, patient overall satisfaction with the mHeart approach was 9 (score 0-10). These findings supported the widespread use of the mHeart in larger research and clinical practice.

- An alarming 36% of the HTx outpatient population were nonadherent to immunosuppressive treatment at baseline according to the SMAQ test, and 41% of patients were unaware of the consequences of forgetting to take their antirejection medicines. These rates confirmed the urgent need for *The mHeart strategy* to deal with this problem.

- *The mHeart strategy* positively impacted on the health outcomes preestablished. At the end of the study, medication adherence rates were statistically significantly improved in the intervention group (85%) versus the control group (46%). Furthermore, the strategy had a positive impact on patients' experience of therapeutic regimens and showed statistically significant reductions in the number of patients needing to travel to the clinic for follow-up appointments. The mHealth approach will be a feasible way to continue providing long-term advanced individually-tailored interventions by health providers to HTx recipients in the at-home setting.

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APPENDIX

APPENDIX 1

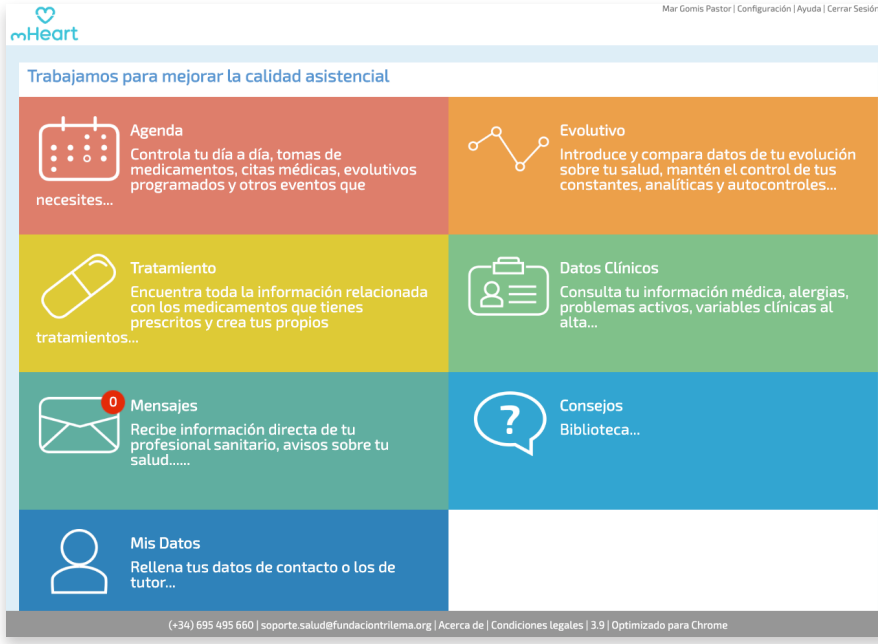
The mHeart system (mobile application and website) screen captures (Version 3.9).

The details of each mHeart module and features are provided in Appendix 6.

mHeart Mobile Application's (App) Main Screen

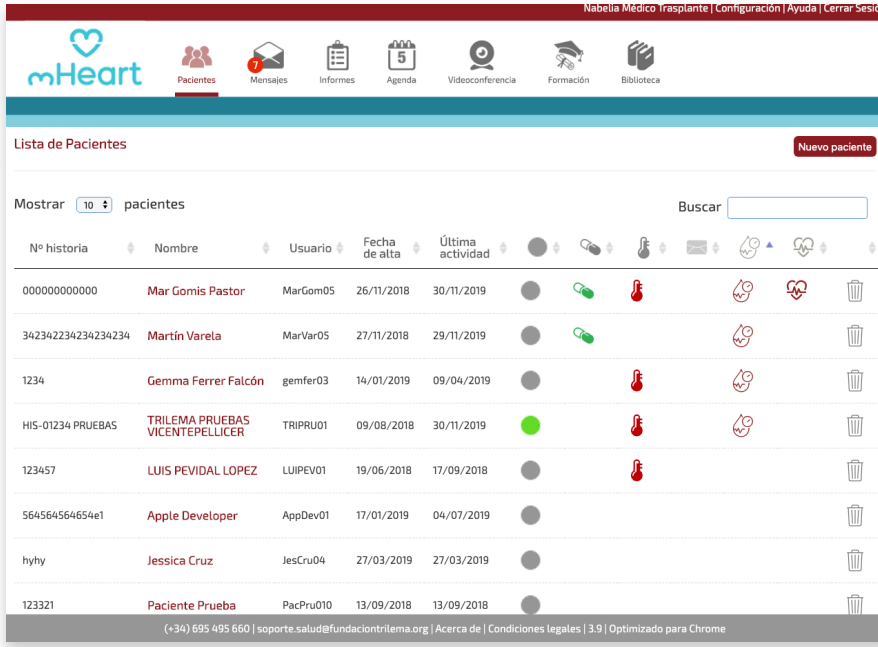
mHeart App Menu

The different App modules are displayed: Treatment, Agenda, Self-control, Symptoms, Messaging, Health Education and Advice, Personal and Clinical Data.



mHeart Website Menu

The different Web modules are displayed: Treatment, Agenda, Self-control, Symptoms, Messaging, Health Education and Advice, Personal and Clinical Data.



mHeart Website Professional Profile

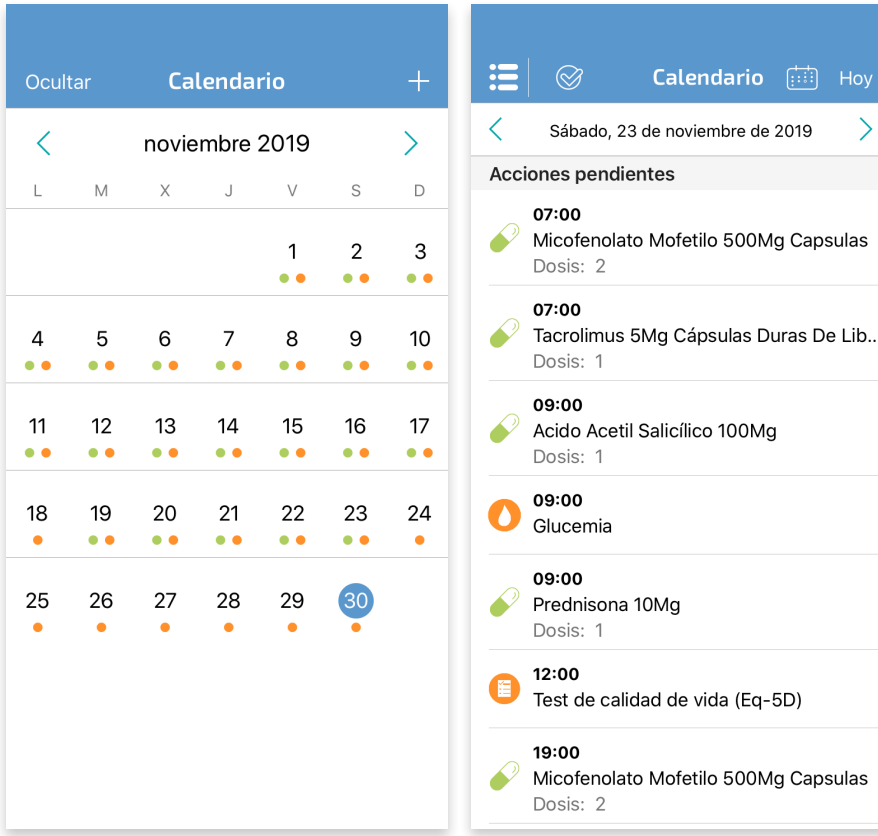
The professional can create a new patient, visualize the complete list of patients, use the messaging module or access each patients' profile. Within each patient profile, there will be a summary of the data entered by patients.

mHeart App 'Treatment' Module: active treatment

When the professional adds active treatment a figure of a stethoscope appears in front of the drug whereas if a patient adds a new therapy, once validated by the professional, a figure of a person appears in front of the drug.

mHeart App 'Treatment' Module: consultation on compatibility between active treatment and new therapies

When adding a new therapy, the patient will choose whether it is a drug or another type of Complementary Health Approach (CHA) (e.g. ginger capsules). The new therapy will show pending until validation by the professional. If the combination is not recommended, it will appear in red, in orange if it is associated with a recommendation and in green if it is accepted without comments.

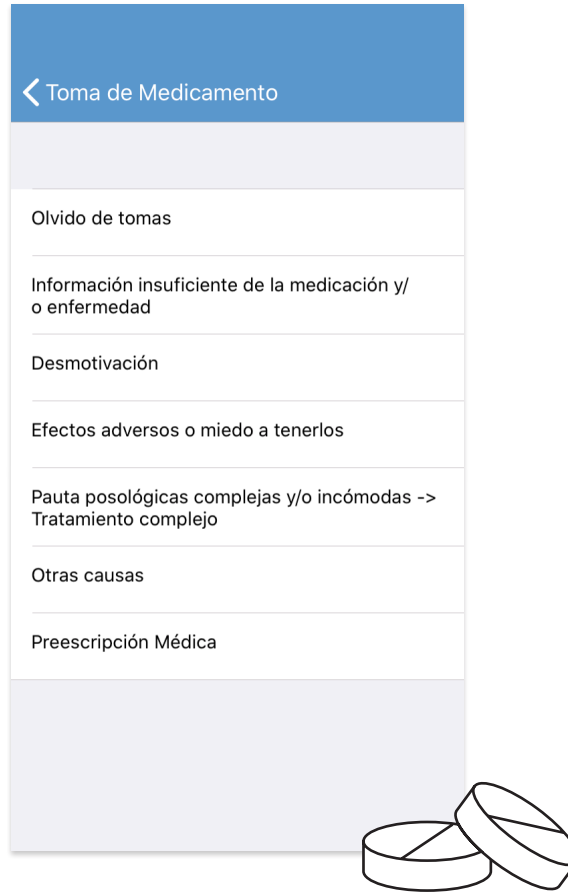


mHeart App 'Agenda' Module: scheduled tasks

The different tasks are shown in different colors in the monthly calendar and in the list of daily tasks: personal events, blood tests, visits, others. These tasks could be introduced by the patient or professional.

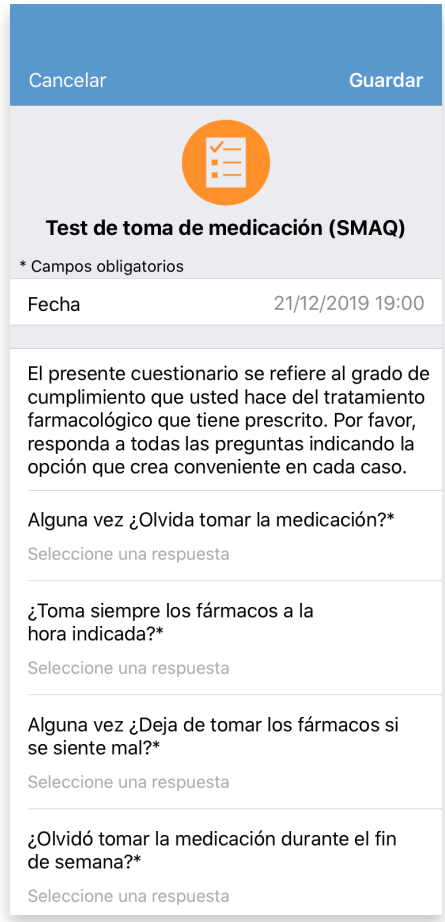
mHeart App Agenda ‘Module’: drug intake confirmation

The patient can confirm or “validate” the intake of a drug individually or several drugs at the same time.



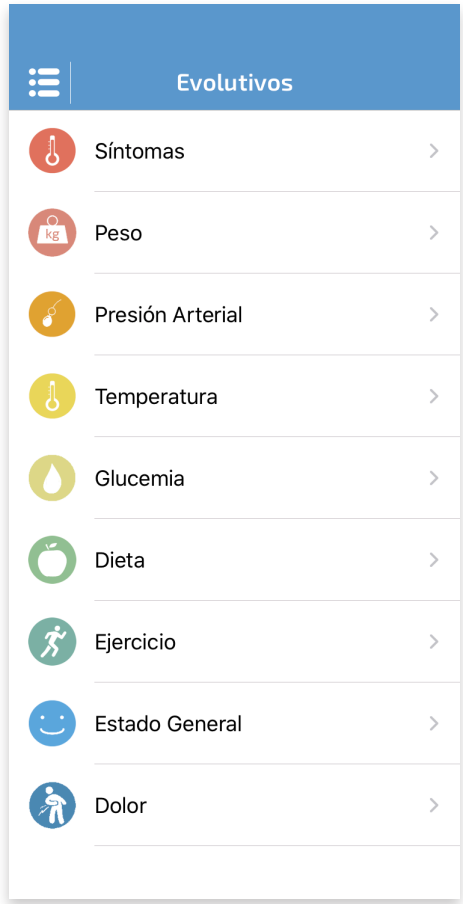
mHeart App 'Agenda' Module: reason for nonadherence

The patient can specify the reason for not complying with therapy: forgetfulness, insufficient information about the dosing schedule and / or illness, demotivation, side effects or fear of suffering them, complex and / or uncomfortable dosing schedules; others.



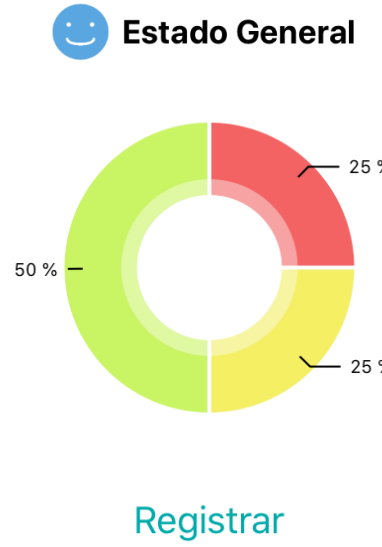
mHeart App 'Agenda' Module: Simplified Medication Adherence Questionnaire (SMAQ) adherence to medications test

Patients can answer the programmed adherence test directly from the agenda.



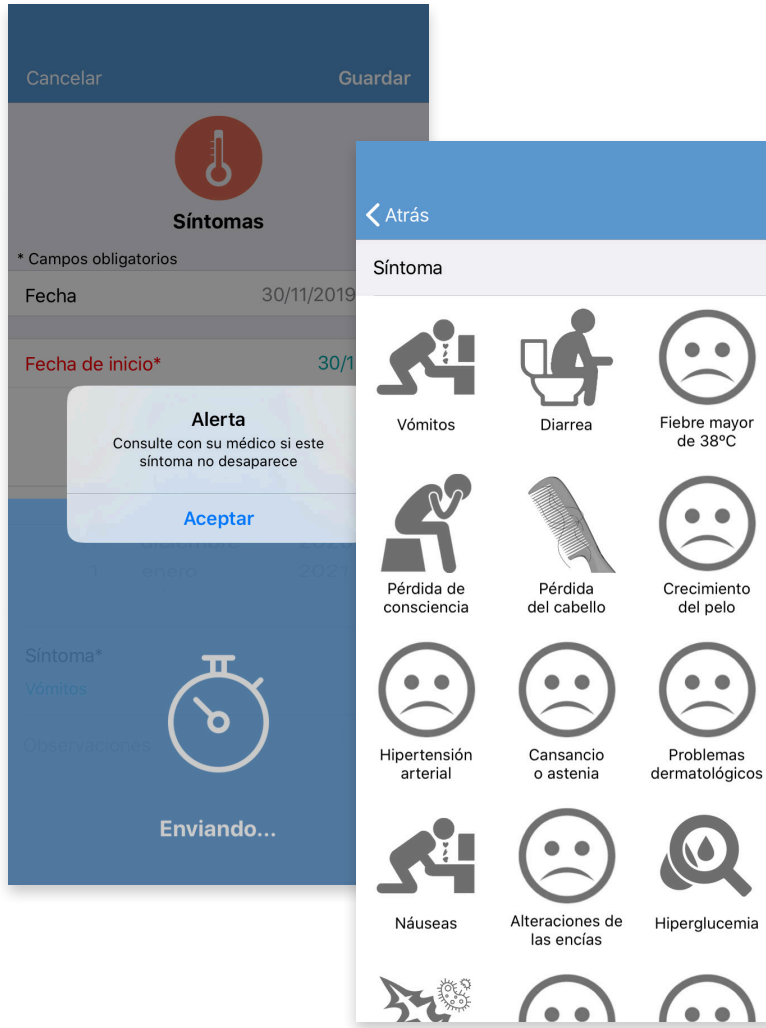
mHeart App 'Self-controls' Module: menu

This module has been adapted for heart transplant patients: diet, exercise, general wellness, cardiac frequency, glycaemia, weight, blood pressure, pain, temperature and symptoms.



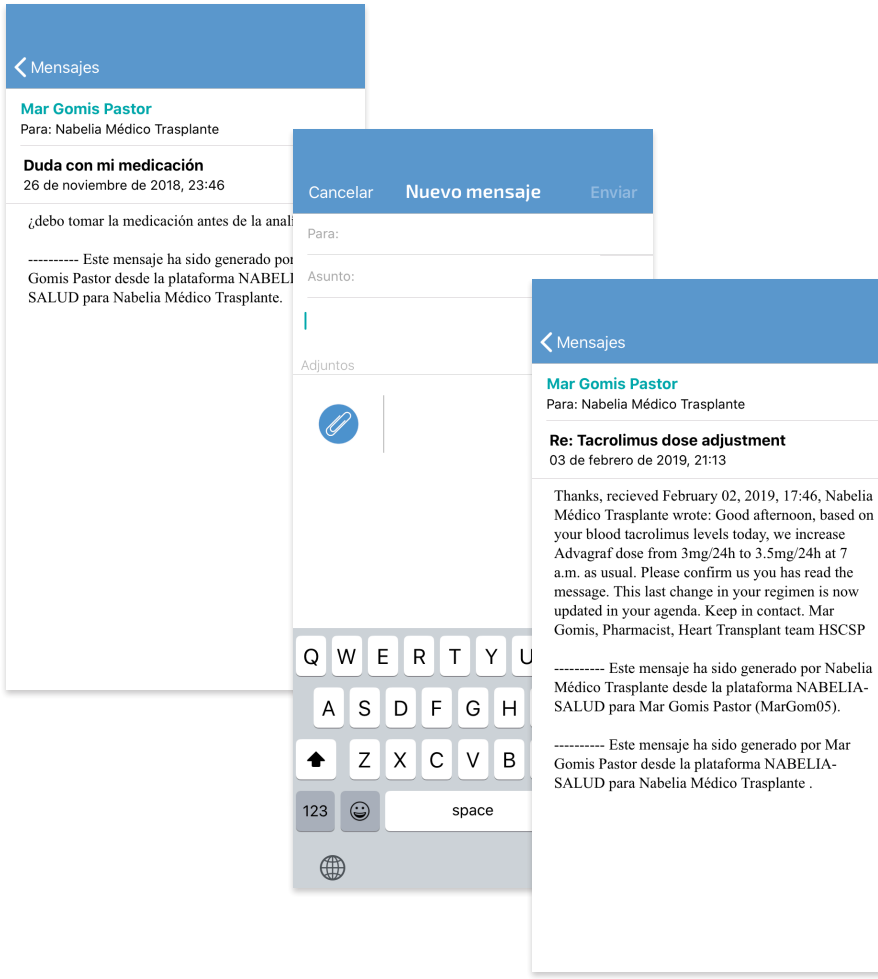
mHeart App 'Self-controls' Module: graphics

Patients can check their progress through a graphic (e.g. blood pressure data or general wellness), introduce a new register or program a test in their agenda.



mHeart App ‘Symptoms’ Module

Patients may register symptoms or side effects related with medication.



mHeart App 'Messages' Module

Patients may send and receive messages from the professionals. An opened or closed envelope symbol appears indicating if the patient has read the email.

mHeart App 'Health Advice' Module

Healthy lifestyle and health promotion information (e.g., texts, photographs, or multimedia files).

mHeart App 'About' Module

Information about the developers, the aim of the tool, and the team in charge of it.

APPENDIX 2

Behavior change techniques designed to improve patients' medication and lifestyle habits and adapted for be delivered using the mHeart platform in interventional studies.

Along with the technique and the theoretical framework, a description is provided to facilitate the selection of the adequate technique according to the clinical aim to be achieved.

Technique[a] (Theory)	Description of the theory-based intervention technique in mHeart
Motivational communication skills (MI)	Use of any patient-provider communication opportunity to prompt the patient to provide self-motivating statements and self-evaluations: (1) minimize resistance to change; (2) maintain the change achieved.
Tailoring	Individualize the interventions provided based on the patient's environment and self-reports.
Provide instructions (SCogT)	Tell the patient how to adopt a health-related behavior, e.g. providers' direct message alerting patients of a prescription change and how to take it.
Time management	Find a timetable for drug intakes and lifestyle habits that fits with each patient's routine.
Goal setting (CT)	Plan together with patients the steps to acquire the skills needed for the new health habit (specifying frequency, intensity, or duration and context).
Provide information (IMB, CT)	Provide information on the behavior-health links and consequences by using the individual or mass campaigns of the mHeart messaging system.
Prompt behavior self-monitoring (CT)	Ask the patient to report data related to distinct behaviors, e.g. drug intakes, side effects, blood pressure, electronic questionnaires, among others PROs.
Provide feedback on performance (CT)	Provide feedback by messaging or in-clinics visit based on the self-reported information to maintain patient enhance with the intervention program.
Provide contingent rewards (OC)	Provide praise or encouragement linked to the achievement of specified behaviors, e.g. praise any improvement in self-efficacy.
Prompt review of behavioral goals (CT)	Review periodically the intentions or goals previously agreed with the patient. Discuss and readjust the plan if necessary.

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Identify barriers to behavior (SCogT)	Identify the barriers to adequate implementation of a new behavior using PROMs, e.g. detect a side effect which is curving adherence to medication.
Action planning & problem solving	Plan ways of overcoming the barriers detected and reach an agreement with the patient, e.g. discuss medication beliefs with the patient.
Environmental restructuring	Provide guidance to change the patient's habits that could hamper the medication or lifestyle behavior.
Teaching the use of prompts/cues (OC)	Teach patients to identify environmental cues to remind them to adopt a behavior.
Prompt intention formation (TRA, TPB, SCogT, IMB)	Encourage the patient to decide to act or set a general goal by making a behavioral resolution, e.g. "I will take my pills on time every day".
Prompting focus on past success	Discuss or review with the patient past behaviors related to negative outcomes.
Others' approval (TRA, TPB, IMB)	Provide information on what others think of a behavior, e.g. inform the patient that providers will disapprove of an unhealthy behavior.
Provide information on others' behavior	Compare anonymous experiences to encourage or reduce the patient's feeling of burden.
Use follow-up prompts	Send messages to the patient after a part of the challenge has been completed. Especially when (1) several goals were planned; (2) a behavior has changed gradually.
Prompt identification as a role model	Indicate how the patient may be an example to others and influence their behavior.

[a] Techniques inspired by the Abraham and Michie's taxonomy (2008).

Abbreviations: PROs, patient-reported outcomes; ROMs, patient-reported outcomes measures.

APPENDIX 3

APPENDIX 3.A

Specific behavior change techniques selected for use during the theory-based intervention program and workflow adapted for delivery using the mHeart platform (*Study 3* and *4*).

Technique (theoretical framework[a])	Description of the behavioral intervention technique and the *element* [b] to support the strategy	Timing[c]	Dose frequency[d]
Motivational communication skills (MI)	Use of any patient-professional communication opportunity to prompt the patient to provide self-motivating statements and self-evaluations: (1) minimize resistance to change; (2) maintain the change achieved. *Element: I,N, M, R, V, C.*	(1) & (2) Adh & N-Adh	(1) & (2) Continuously
Tailoring	Use any opportunity to individualize the management of adherence to a specific patient, based on the patient's environment and self-reports. *Element: all.*	Adh & N-Adh	Continuously
Provide instructions (SCogT)	Tell the patient how to adopt a medication-related behavior, i.e. (1) education on the importance of taking immunosuppressive medication and management of side effects. *Element: I, M, C*; (2) responses to the patient's queries and doubts. *Element: M*; (3) information about the prescription change (doses, drug, etc.) and explaining the reason for the change. *Element: M,C, N*.	(1), (2) & (3) Adh & N-Adh	(1) Baseline & If Need (2) & (3) Continuously
Time management	(1) Find a time for intake that fits with each patient's lifestyle. Include this schedule in the patient's mHeart agenda and activate intake alarms if necessary. (2) Train him/her on what to do if intake is late. *Element: A, M, I*	(1) & (2) Adh & N-Adh	(1) & (2) Baseline & If Need
Goal setting (CT)	Involve the professional and recipients in detailed planning of the steps the patient will take to acquire the medication skills needed for adequate medication adherence (frequency, intensity, duration and context). *Element: all.*	Adh & N-Adh	Baseline & If Need

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Technique (theoretical framework[a])	Description of the behavioral intervention technique and the *element* [b] to support the strategy	Timing[c]	Dose frequency[d]
Provide information on the behavior-health link (IMB)	Consider providing general information by mass campaigns about behavioral risk, i.e. (1) importance of taking immunosuppressive drugs on time, (2) reminding patients about sun protection adherence. *Element: M*	(1) & (2) Adh & N-Adh	(1) Baseline & W2 (2) W2
Provide information on the consequences (CT)	Inform the patient of the benefits and costs of changing or not changing a behavior (i.e. adherence or nonadherence to medications or monitoring). E.g. pressure rates on range if adhere to antihypertensives. *Elements: M, C, I, R, V*	Adh & N-Adh	Once/week & If needed
Prompt self-monitoring of behavior (CT)	Prompt patient to report data related to medication behavior, i.e. (1) drug intake in the agenda; (2) medication adherence ePROMs; (3) side effects; (4) glycemia, blood pressure, etc. *Elements: L, M, V, R, P, N*	(2), (3) & (4) Adh & N-Adh (1) N-Adh	(1) (2) (4) Continuously (3) If need
Provide feedback on performance (CT)	Provide the patient with data based on the self-reported information to maintain patient motivation and adherence with the intervention program, i.e. (1) biomeasures pattern; (2) side effects; (3) medication adherence ePROMs; (4) medication intake. *Elements: P, R, V, M*	(1), (2), (3) & (4) Adh & N-Adh	(1) & (4) Once/week (2) If needed (3) Continuously
Provide contingent rewards (OC)	Provide praise or encouragement linked to the achievement of specified behaviors, e.g. praise any improvement in self-management. *Elements: P, R, V, M*	Adh & N-Adh	Continuously
Prompt review of behavioral goals (CT)	Review the intentions or goals previously agreed with the patient; discuss and readjust the plan if necessary. *Elements: M, C*	N-Adh	Once/week & If need
Identify barriers to behavior (SCogT)	Identify the barriers to adequate adherence using PROMs, e.g. detect a specific side effect reported by the patient electronically. *Elements: R*	N-Adh	If needed
Action planning & problem solving	Plan ways of overcoming the barriers detected and reach an agreement with the patient, e.g. discuss medication beliefs with the patient. *Elements: all*	N-Adh	If needed

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Technique (theoretical framework[a])	Description of the behavioral intervention technique and the *element* [b] to support the strategy	Timing[c]	Dose frequency[d]
Environmental restructuring	Provide guidance to change the patient's habits that could hamper medication adherence. *Elements: all*	N-Adh	If needed
Teaching the use of prompts/ cues (OC)	Teach the patient to identify environmental cues to remind him/her to adopt a behavior, i.e. (1) times of meals could serve as reminders of medication intake; (2) a beeping signal at the time of scheduled medication intake. *Element: A, P, M*	N-Adh	Baseline & If needed
Prompt intention formation (TRA,TPB, SCogT, IMB)	Encourage the patient to decide to act or set a general goal, e.g. to make a behavioral resolution such as "I will take my pills on time every day". *Element: I, N, L, M, V*	N-Adh	If needed
Prompting focus on past success	Discuss or review with the patient past behaviors related to negative outcomes. *Element: M, C, V, R*	N-Adh	If needed
Others' approval (TRA, TPB, IMB)	Provide information on what others think of a behavior, i.e. inform the patient that professionals will disapprove of an unhealthy behavior. *Element: M*	Continuously N-Adh	If needed
Provide information on others' behavior	Compare anonymous experiences, e.g., compare the patient's prescription with another significantly more complex regimen to reduce his/her feeling of burden. *Element: M, V*	N-Adh	If needed
Use follow-up prompts	Communicate the patient if a part of the intervention is complete, i.e. (1) several goals were planned; (2) a behavior has changed gradually. *Element: all*	(1) & (2) N-Adh	If needed
Prompt identification as a role model	Indicate how the patient may be an example to others and influence their behavior, e.g., offer a patient to be part of the voluntary service. *Element: M*	Adh	W3

[a] The theoretical frameworks are: CT, control theory; IMB, information-motivation-behavioral skills model; MI, Motivational Interview; OC, operant conditioning; SCogT, social-cognitive theory; TPB, theory of planned behavior; TRA, theory of reasoned action.

[b] Elements (i.e. components or objects of the technology intended to implement the strategy) used in the study: (A) alerts, (P) prompts/reminders, (N) notifications, (M) messages, (L) logs, (R) reports, (V) visualizations, (C) video-calls, (I) Information delivery. (154,159)

[c] Nonadherence to medication in the implementation phase is defined as "actual dosing does not correspond to the prescribed dosing regimen due to delays, omissions or extra doses" and is measured by self-report questionnaires. Delays refer to irregularities with the intake schedule (±2 hours).

[d] Definitions: Baseline: when the treatment begins; Continuously: every time the task is scheduled during the treatment period between assessment 1 and 2; If Need: when provider detect that the strategy is needed based on reports or goals established; Once/week: at least 1 time per week based on reports; W1: during week 1 of the study; W2: during week 2 of the study; W3: during week 3 of the study.

Abbreviations: Adh., medication-adherent recipient; ePROMs, electronic patient-reported measures; N-Adh., only if the patient is classified as nonadherence to medication (implementation phase).

APPENDIX 3.B

Description of mHeart-based treatment designed to improve medication adherence in the Val-mHeart study.

The information complements the data in the Val-mHeart manuscript. For more information, please consult *Study 3* Methods.

Specific aim of the treatment

- The treatment is defined as the interventional program applied in this study based on multiple internet-based strategies or interventions to achieve the clinical aim.
- The clinical aim of the treatment in the Val-mHeart study was to optimize medication adherence management in early-stage HTx recipients, i.e. to reduce the rate of nonadherent recipients.

Treatment duration

- A period of at least 1 month (between assessments 1 and 2).

Type of treatment

- The e-interventions were interactive with additional human support through the mHeart platform.
- The provider was a female clinical pharmacist with experience in motivational interviewing and specialized in the heart transplant population. The patients' first interaction with this provider was during hospitalization for the transplant procedure. No other contact was provided on-site after the first baseline study visit.
- The patients' characteristics are described in the manuscript, including the training and technical assistance received.

Delivery platform

- The hardware platform delivers the intervention via mobile platforms such as smartphones. Patients had access to a complementary website via desktop computers. Providers manage the platform through the website.

- Participants used their own cell phone and paid for their internet use. No incentives were provided for participation.

- The mHeart software (mobile application and website) is a Behavior Intervention Technology to facilitate the following overall goals: (1) health behavior change (i.e. increase patients' healthy behaviors and prevent the onset of disease); and (2) targeted disease management (i.e. facilitate therapeutic interventions and improve patients' self-management).

- The features specifically designed to manage medication adherence are provided in the manuscript. Other components or functionalities are detailed in a video of the mobile application provided in [Dataset] (1).

- More information on developers, technical specifications and Source Code are provided in [Dataset] (1).

Presentation strategy

- The mHeart platform is based on visual aids and minimizing text and passive information. For readers to have a clear sense of the aesthetics, visual aids used and other features, they were provided with a video with a demo trial of the clinical use of the app. Thus, readers can examine samples or portions of eHealth interventions through mHeart.

- Interactive **elements** were also used as digital **triggers** to prevent the law of attrition; i.e. (A) alerts, (P) prompts and reminders, (N) notifications, (M) messages, (L) logs, (R) reports, (V) visualizations, (C) video-calls, (I) information delivery. (154,159)

Content

- The interventional treatment **design** was based on published literature on internet-based interventions with impact on health behavior change, but also strategies to prevent patient attrition. (129,141,147,153,174–177)
- All the **behavioral change techniques** (86,87) used in the treatment are described based on Michie's taxonomy (146) and are provided in the Appendix 3.A. The most **important strategies** applied were human support, motivational engagement, therapeutic alliance strategies, (75,159) and individually-tailored feedback. (86,87,155,156,178) **Descriptions** of the strategies and examples are provided in the Appendix 3.A.
- The strategy could be aimed at (1) forming a behavior; (2) altering a behavior (3) reinforcing a behavior.
- The interventions were **tailored** based on mHeart patient-reported data collected using (1) dynamic information from the mHeart features, and (2) information collected in the in-clinic baseline interviews.
- Interventions were **delivered** using motivational interviewing skills. (90,91)

Workflows

- **Intended doses** and **optimal timing for the use** of each technique are also described in the Appendix 3.A.
- **Conditions of use**, a mixture of time-based, event-based or task-completion rules were applied as required. (169) Thus, the **complexity** of the strategies varied depending on the user and the task. A combination of these techniques was common.
- Video calls were not scheduled and were limited to very occasional situations when a text message was insufficient to deliver highly complex information.

APPENDIX 4

Methodology used to measure validity properties of the electronic PROMs to assess medication adherence in the at-home setting using the mHeart platform in HTx recipients (*Study 3*).

Definition of the measurement property[a]	Statistical analysis[a]		Study method
Content validity. The degree to which a PROM includes the most relevant aspects of a concept in the context of a given measurement application. (84)			
The validity in this study begins with the adequate representability and relevance of the questionnaires selected by the experts to measure medication adherence[b] by the mHeart platform.	The inter-rater agreement between the expert panel (191,245) was calculated based on the Group Consensus Method. (246) Agreement measurement: (i) percentages of agreement. Agreement among >75% of the expert panel was considered adequate. (ii) *P*-value on-side to test if *P* was greater than 0.75% – 75%. A greater *Proportion* implied greater agreement between experts.		The expert panel consisted of 14 health professionals including 3 nurses, 7 cardiologists and 1 pharmacist of the heart failure and HTx unit, as well as 1 pharmacist specialized in medication adherence and 2 clinical pharmacists with experience in in-clinic motivational interviews. The pharmacists proposed 3 medication adherence PROMs broadly used in in-clinic practice: the Haynes-Sackett, (197) Morisky-Green-Levine (199) and the SMAQ (203) questionnaires. The selection of 2 of them for implementation in the mHeart tool had to be based on: adequacy of the PROMs to be performed through an app, validation and experience of use of the PROMs, and the degree to which the instruments measure complementary constructs of medication adherence. The experts were asked to evaluate these criteria and whether the suggested PROMs were adequate for implementation in the mHeart platform. The discussion was verbal and panel members voted by rising their hands.
The degree to which the new 6 difficulties with medication implemented in the Haynes-Sacket ePROM are an adequate reflection of the construct to be measured.	The inter-rater agreement among the expert panel (191,245) was calculated based on the Nominal group consensus method. (246) Agreement measurement: Same as above.		The same expert panel was asked to evaluate by written record if they agreed (Yes/No) with different criteria for each of the 6 medication difficulties of the Haynes-Sacket ePROMs. Afterward, a moderated verbal discussion took place. ▪ Useful to evaluate medication adherence ▪ Intuitive ▪ Brief (can be completed rapidly) ▪ Patient-friendly language
The degree to which the items of the ePROM itself are an adequate reflection of the construct to be measured compared with the original in-clinic PROM.	The inter-rater agreement among the expert panel (191,245) was calculated based on the Nominal group consensus method. (246) Agreement measurement: Kappa coefficient calculated for the overall PROM score and for each item.		The same expert panel was asked to evaluate by written record if they agreed (Yes/No) with several characteristics of the electronic version compared with the in-clinic PROM. Then, a moderated verbal discussion took place. ▪ True to the original text ▪ Useful to evaluate medication adherence ▪ Intuitive ▪ Brief (can be completed rapidly) ▪ Patient-friendly language
Convergent validity			
The degree to which the Morisky-Green-Levine PROM score is consistent with other instruments based on the assumption that measures the same construct.	Positive correlation with another instrument measuring the same construct. Correlation measurement: Phi coefficient.		To assess the correlation of the scores between the Morisky-Green-Levine PRO, both electronic and in-clinic, with the in-clinic SMAQ (203) instrument. The SMAQ questionnaire was adapted from the Morisky-Green-Levine and validated in the transplant population as an adequate reflection of the dimensionality of the construct of adherence to be measured.
Discriminant validity (divergent validity)			
The degree to which the Haynes-Sacket PROM score is not consistent with other instruments based on the assumption that this PROM measures another construct.	Negative correlation or lack of correlation between PROMs measuring different constructs. Correlation measurement: Phi coefficient.		To assess the differences in the scores between the ePROMs implemented in the platform (Haynes-Sacket vs Morisky-Green-Levine), since the information provided by the 2 instruments are different and complementary. The same comparison was made using the SMAQ PROM, which measures different adherent constructs of the Haynes-Sacket construct of adherence.

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Definition of the measurement property[a]	Statistical analysis[a]		Study method
Reliability or reproducibility. The degree to which a PRO instrument is free from measurement error. (84,247)			
The degree to which the 2 versions of the same test (the electronic and in-clinic adherence PROMs) measure the same construct.	Equivalent forms reliability method. (191) Measure of association: Phi coefficient (reliability coefficient).		To ask to the same group of patients and on the exact same day to independently perform the in-clinic PROMs and the mHeart ePROMs. To assess the association between score versions of the electronic PROMs or the in-clinic PROMs.
The extent to which the scores of the test are consistent for repeated measurement over time in patients who have not changed (score stability measurement).	Test-retest reliability method. (191) Agreement measurement: Kappa coefficient (210) (stability or reproducibility coefficient).		To ask patients to complete the ePROMs 7 days after the last completion. The patients must remain clinically and therapeutically stable during this 7-day period to be included in the test-retest analysis. To compare the ePROMs scores obtained in Assessments 2 and 3. The 7-day gap was selected to minimize the effect of possible confounding variables (210) related to the multifaceted factors affecting the patient's medication adherence post-transplant. (79) Intervals of 1-2 weeks appear to be typical in reproducibility of health status measures. (236)
Responsiveness or sensitivity to change			
The responsiveness or sensitivity to change is the ability of the PROM to detect change over time in the construct being measured.	Percentage of adherent and nonadherent recipients. Measurement: Statistical test to calculate the change in significance of *P*-values.		To measure the medication adherence PROMs overall scores for each visit. To calculate the improvement in medication adherence between assessments, as a measure of the intervention effect. The follow-up time between visits was at least 4 weeks. The validity of an indirect measures is adequate if it includes 1-month periods. (204) Smartphone use cycles with a time gap of 4 weeks between them are highly likely to be independent cycles. (205)
Interpretability			
The degree to which easily understood meaning can be assigned to an instrument's score and the meaningful level of change.	Measurement by 3 aspects: 1. Score interpretation. 2. Meaningful change. 3. Comparison of scores in the transplant population.		To respond to the following questions: 1. Are the scores easily interpreted? 2. What does a high or low score represent? 3. Is the baseline rate different or similar to that of other studies? 4. What comprises a meaningful difference in the score compared with other series in transplant populations?
Respondent burden			
Burden is defined as the time, effort, and other demands placed on respondents who are administered the instrument.	The SAC-MOS guidelines (152) recommendations suggests various review criteria for respondent burden.		To analyze the following criteria with the ePROMs versus the in-clinic PROMs from the respondents' point of view: 1. Average and range of time needed to complete the instrument. 2. The level of comprehension needed for the population. 3. Indication of when or under what circumstances the instrument is not suitable for respondents. 4. The acceptability of the instrument by indicating the level of missing data and the reasons. 5. Provision of evidence that the instrument places no undue physical or emotional strain on respondents.

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Definition of the measurement property[a]	Statistical analysis[a]		Study method
Administrative burden			
Burden is defined as the time, effort, and other demands placed on persons administering the instrument.	The SAC-MOS guidelines (152) suggest various review criteria for administrative burden.		To analyze the following criteria with the ePROMs versus the in-clinic PROMs from the administrative point of view: 1. Resources required for administration of the instrument. 2. Special requirements such as the need to record the results into the HIS or EHR. 3. The average time and range of time required by a trained interviewer to administer the instrument in face-to-face interviews or through the mHeart platform. 4. The amount of training needed, and level of education or professional expertise and experience needed to administer, score or use the instrument. 5. The availability of the scoring instructions for the PROMs.

[a] The definition of the properties, statistical analysis and methodology was adapted to this study based on the SAC-MOS Guidelines, the COSMIN consensus and the ISOQOL standards.

[b] Nonadherence to medication in the implementation phase was defined as "actual dosing does not correspond to the prescribed dosing regimen due to delays, omissions or extra doses" and was measured by self-report questionnaires. Delay refers to irregularities in the intake schedule (±2 hours).

Abbreviations: EHR, health electronic records, ePROMs, electronic patient-reported outcome measures identified by the mHeart tool; HIS, hospital information system; in-clinic PROMs, patient-reported outcome measures identified by a face-to-face interview in the clinic; PROMs, patient-reported outcome measures.

APPENDIX 5

Suggested person-centered interventions, features needed to perform such interventions, and case examples to simplify regimens in the solid organ transplant population.

Person-centered Interventions	Examples
Simplifying the number of doses per day	
Using drug combinations in one pill.	Consider combinations of antihyperlipidemic agents or antihypertensive treatments.
Reduce frequency	
Using sustained-release or long-acting formulations.	Consider extended-release tacrolimus instead of immediate-release tacrolimus when possible.
Making administration requirements easier	
Coordinating doses with patients established daily routines.	Recommend taking the medication with meals at the same time every day.
Avoiding non-dairy regimens.	Avoid >48-hour regimens or different doses depending on the day.
Suggesting a self-management weekly pill box in recipients able to manage their treatment.	Specially recommended in recipients with complex daily routines (e.g. working or taking care of children) or overwhelmed by complex regimens regardless of their age.
Suggest applying for medication management and pillbox programs by local pharmacist.	Recommended in recipients unable to be in charge of their medications for any reason (e.g. cognitive impairment, vision problems, older people mixing up medications, etc.)
Considering non-pharmacologic alternatives	
Introducing lifestyle recommendations, exercise, psychological therapy, mindfulness techniques, among other complementary therapies.	Safe and useful alternatives may be used to achieve benzodiazepine withdrawal. Consult with a pharmacist to confirm compatibility of supplements or herbal options.

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Person-centered Interventions	Examples
Deprescribing chronic treatments or substituting them	
Considering if a nonessential chronic drug is prescribed over the years.	Consider suspending proton pump inhibitors in recipients <65 years without other risk factors (i.e. chronic diseases or drug combinations) and symptoms.
Considering if a chronic drug is currently unnecessary, depending on the patient's ever-changing clinical situation.	Consider measuring urate after transplantation in patients treated with allopurinol before the transplant.
Considering a substitute when treatments seem to be ineffective or not useful depending on the patient's current clinical status.	Chronic antidepressant withdrawal in stable patients taking this medication since the transplant may be considered by the clinician.
Avoiding prescribing cascade	
If a prescribing cascade is identified, professionals should consider discontinuing the treatment or prescribing an alternative to the drug related to the negative event.	A prescribing cascade occurs when a new drug is used to treat an adverse event caused by another drug. An example of a prescribing cascade is prescription of diuretics to treat edema caused by calcium antagonists, or prescription of laxatives in patients with constipation caused by calcium supplements.

APPENDIX 6

MHeart® patient a professional profile modules, components, and clinical use.

mHeart images are provided in Appendix 1.

Patient Module	Components and clinical use
Treatment	Medication list including information on inactive drugs. Enquire about interactions consultation (i.e. ask transplant pharmacist about new therapies).
Patient-Centered Module	Consulting and recording data (manually or using wearables). Reminders can be scheduled in *Agenda*. 1. Vital signs (i.e. blood pressure, temperature, pulse and respiratory rate) and biomeasurements (i.e. weight, height, glycemia). 2. Dietary intake, exercise data, and general wellness. 3. Health instruments: adherence to medication (Haynes-Sackett (198) and Morisky-Green 4-item scale (248)), insomnia (Insomnia Severity Index (249)) and quality of life (EQ-5D-3L (250)). 4. Symptoms or adverse effects. The symptoms connected with an alert to clinicians were diarrhea, vomiting, fever, fainting episode, and syncope.
Agenda	The content of diverse modules is uploaded. A Push text alert can be activated on the patient's mobile phone. 1. Medication timing and consultation of recommendations. 2. Drug intake recording (single or several drugs at the same time) and reasons for nonadherence (drop-down list). 3. Non-pharmacological prescriptions (e.g. relaxation practice according to the psychologist's prescription). 4. Tasks from the *Patient-Centered Module* programmed (e.g. blood pressure monitoring 3 times per week). 5. Health reminders (e.g., appointments, blood tests).
Communication Aids	1. Teleconference: individual and group sessions. 2. A private patient-provider chat. Files can be attached.
Health Advice	Healthy lifestyle and health promotion information (e.g., texts, photographs, or multimedia files).
Personal and Clinical Data	Sociodemographic data, documented allergies and provider profiles (including affiliation and picture).

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Patient Module	Components and clinical use
Help	1. A help center service to solve both technical and functional problems (i.e. telephone number, private message, and email). 2. Clinical contact data: medical team, pharmacist, transplant coordinator, patient appointment center, etc.
About	Information about the developers, the aim of the tool, and the team in charge of it.
Terms of Use and Privacy Policy	All the legal requirements already accepted should always be available for consultation.
Provider Module	**Component and clinical use**
Patient View	List of active patient filters to organize the list and perform a rapid search.
Patient Registration	The Center identification number is used to download patient data from the hospital information system. The patient receives a private message with login credentials. Providers individualizes the patient-reported outcome measures schedule and the treatment plan and recommendations for each new patient.
Treatment Prescription	Pharmacological treatment is prescribed from a drop-down list of drugs updated from the Spanish National Formulary. Tailored recommendations can be added (e.g. "Anti-rejection treatment. It is recommended that you take this on an empty stomach"). Non-pharmacological therapies can be prescribed in free-form data entry by the multidisciplinary team (e.g. non-salty diet).
Patient-Centered Data Consultation	All the data recorded in the *Patient-Centered Module* can be tracked graphically in tables and diagrams. Timeframes filters can be used. mHeart® platform features designed to follow medication adherence are adherence test results and drug intake registrations: A traffic light system alerts provider of a decrease in the patient's weekly adherence. List of patients can be sort by adherence rate to prioritize interventions. Adherence rates are presented graphically and through tables (for each drug and for the overall treatment).
Communication Aids	Individual patient-provider chat. Group messaging. Filters are available. Large-scale interventions can be scheduled (e.g. preventive health promotions) for specific time periods. Teleconsultation patient/s-provider/s for individual or group visit. Teleconference for interdisciplinary communication and shared decision-making between providers.

APPENDIX 7

Main areas for improvement in mHeart Prototype 1 as a result of user feedback during Alpha testing (*Study* 2).

General Settings	
Patient	▪ Improve visualization of the menu login button. ▪ Provide direct messaging for contacting the developer's technical team.
Provider	▪ Adapt the Web to a responsive design. ▪ Modify the user password every 3 months by an automatic message. ▪ Avoid manual input of patient data on discharge. ▪ Supply the legal conditions of use that the patient accepts. ▪ Decrease the number of seconds needed to access the app. ▪ Multi-device access to the patient's app (e.g. if caregivers need to be included). ▪ Include a provider monitoring section from which vital signs registered in follow-up (blood pressure or analytical data) can be consulted and downloaded in Excel format.
Personal and Clinical Data Module	
Patient	▪ Provide health professional job profiles in the clinical team list. The profile also would be visible when the patient selects the recipient of a message (e.g. Name Surname Pharmacist).
Provider	▪ Include a summary heading with each patient's main data, together with a photograph. ▪ Consult the information recorded by a patient in the clinical history available in any center in the health area.
Treatment Module	
Patient	▪ Consult with the HTx team about any incompatibility with courses of treatment prescribed by other providers in the health area. ▪ Facilitate queries referring to other complementary treatments. ▪ Retrospectively validate drug intake and allow multiple validations at the same time.
Provider	▪ Improve diverse aspects of the drug prescription module to make it quicker and more user-friendly.

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Agenda Module	
Patient	▪ Add photographs of drug packaging to identify it.
Provider	▪ Change the main screen of the app to the Agenda directly. Change the main screen of the website to the Modules list. ▪ Modify the color of the icons to differentiate the distinct types of notification tasks. ▪ Include another type of reminder on the list: “tests” and “visits”.
Patient-Centered Outcomes Module	
Patient	▪ Include a function to monitor glycemia and temperature. ▪ Improve visualization of the rating of perceived physical exertion (using the Borg Scale).
Provider	▪ Modify the adherence graph for easier viewing of responses. ▪ Modify the patient-reported outcome data charts to include the average maximum and minimum for the time indicated. ▪ Modify the charts to automatically incorporate data corresponding to the last month.
Symptoms Module	
Provider	▪ Include email alerts related to extremely serious symptoms notified by patients via the platform and new courses of treatment included by the patient. ▪ Add “vomiting” as a very serious symptom.
Health Education and Advice Module	
Patient	▪ Provide post-transplant lifestyle and dietary recommendations.
Provider	▪ Add recommendations and advice using videos.
Teleconsultation and Messaging Module	
Patient	▪ Enable archives to be uploaded in messages.
Provider	▪ Permit to send provider campaigns through the messaging system by text-messages in bulk to all patients or to a group of them via filters.

APPENDIX 8

Results of the online survey on usability and satisfaction with the mHeart platform and intervention implemented during the study period in HTx recipients.

Table A shows the categorical variables and Table B the quantitative variables (N=29).

Table A. Categorical variables, N(%)	
I usually use the platform through:	
Mobile application (app)	26 (90)
Webpage	2 (7)
Both equally	1 (3)
My frequency of use of the mHeart mobile app is:	
I don't use it	0 (0)
Occasionally	2 (7)
Every 15 days	1 (4)
Every week	4 (14)
2 or 3 times a week	3 (10)
Every day	19 (66)
I've looked the Health Advice Module through the platform:	
Never	5 (17)
Between 1 and 5 times	18 (62)
More than 5 times	6 (21)
What information would I like to see in the Health Advice Module: (more than 1 answer is allowed)	
Information videos made by HTx staff	19 (66)
Medical advice website on transplants	8 (28)
Medical advice website on health in general	8 (28)
Transplant protocols	1 (3)
Other	4 (14)
Don't know/no answer	3 (10)
To find out whether I can take a new therapy (drug, herbal, infusions, homeopathy, etc.) I use: (more than 1 answer is allowed)	
The "new treatment" feature of the platform	6 (21)
The platform's chat system	19 (66)
Telephone, I ring the pharmacist	15 (52)
Telephone, I ring the doctor	0 (0)
I haven't had to make any enquiries	3 (10)
I don't know/no answer	0 (0)

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Table A. Categorical variables, N(%)	
Since I've been using the platform, I feel: (more than 1 answer is allowed)	
Supported by my healthcare team	18 (62)
More secure because I can clear up my doubts	23 (79)
More in control of my health in general	9 (31)
Overloaded by the tasks in the platform	1 (3)
Overwhelmed by the messages from my healthcare team	0 (0)
Other (free field)	0 (0)
Would I recommend using the platform to other transplant recipients?	
Yes, I'd recommend its use	29 (100)
No, I wouldn't recommend its use	0 (0)
Thank you for your honesty. Please say why you wouldn't recommend using the platform	-
Do you have any suggestions for improving the platform?	
No, I like it just as it is	22 (76)
Other (free field):	7 (24)
Patient 1: *"Some things should be improved".*	-
Patient 2: *The questions on the attitude to medication are always the same and in the same order. This makes us not pay attention when we've given more than two responses. I think the order should be mixed up.*	✓ Improved
Patient 3: *Problems with messages and alerts about intakes in the mobile app make the app not useful.*	✓ Improved
Patient 4: *Registration of medication intake could be per day or like now.*	Explained to the patient
Patient 5. (A) *To record blood pressure, you first have to delete the numbers that appear and sometimes it's quite difficult because the keys and the cursor arrow appear on the screen at the same time.*	✓ Improved
Patient 5. (B) *What can you do if you realize you've made a mistake in a number that you've already sent?*	Explained to the patient
Patient 6: *It would be better to send alerts of a new message, without the patient having to go to the update button.*	✓ Improved
Patient 7: *I'd like to see the graphs on my mobile .*	✓ Improved

Table B. Quantitative variables, N(%)	1	2	3	4	5	6	7	8	9	10	DN/NA	Mean±SD (0 to 10 score)
I find the use of the platform and its general functioning: *1. Very difficult ☹ 10. Very simple ☺*	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	2 (7)	1 (4)	8 (28)	3 (10)	13 (45)	0 (0)	9 ± 2
The username and password to access the platform are simple and easy to remember: *1. A little ☹ 10. A lot ☺*	6 (21)	0 (0)	0 (0)	1 (4)	3 (10)	1 (4)	2 (7)	2 (7)	3 (10)	11 (38)	0 (0)	7 ± 4
The initial telephone training I received from mHeart on the use of the platform was: *1. Not very useful ☹ 10. Very useful ☺*	0 (0)	0 (0)	1 (4)	1 (4)	1 (4)	4 (14)	3 (10)	4 (14)	4 (14)	10 (35)	1 (4)	8 ± 2
When I've had doubts and/or incidents, mHeart 's Help Center has been: *1. Not very useful ☹ 10. Very useful ☺*	0 (0)	0 (0)	0 (0)	2 (7)	1 (4)	2 (7)	4 (14)	5 (17)	2 (7)	12 (41)	1 (4)	8 ± 2
When I record my weight, blood pressure, heart rate, etc., on the platform, it motivates me to look after my health: *1. A little ☹ 10. A lot ☺*	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	2 (7)	3 (10)	3 (10)	3 (10)	15 (52)	1 (4)	9 ± 2
Recording my weight, blood pressure, heart rate, etc. on the platform is: *1. Difficult ☹ 10. Simple ☺*	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (10)	5 (17)	2 (7)	18 (62)	1 (4)	9 ± 1
The alerts in the Agenda Module to remind me to record my blood pressure, weight, heart rate, etc., are: *1. Annoying ☹ 10. Helpful ☺*	0 (0)	0 (0)	1 (4)	1 (4)	0 (0)	2 (7)	2 (7)	6 (21)	5 (17)	11 (38)	1 (4)	8 ± 2
If I have a side effect, I record it in the Symptoms Module of the platform: *1. Never ☹ 10. Always ☺*	6 (21)	1 (4)	2 (7)	4 (14)	1 (4)	2 (7)	2 (7)	2 (7)	1 (4)	5 (17)	3 (10)	5 ± 3
Registering my symptoms in the platform is: *1. Difficult ☹ 10. Easy ☺*	1 (4)	0 (0)	1 (4)	1 (4)	2 (7)	0 (0)	4 (14)	3 (10)	2 (7)	12 (41)	3 (10)	8 ± 2.5
The health Advice Module of the platform is: *1. Not very useful ☹ 10. Very useful ☺*	0 (0)	0 (0)	1 (4)	0 (0)	4 (14)	4 (13)	3 (10)	5 (17)	0 (0)	9 (31)	3 (10)	8 ± 2
Registering whether I take my medication in the Agenda Module is: *1. Annoying ☹ 10. Helpful ☺*	0 (0)	1 (4)	0 (0)	0 (0)	2 (7)	3 (10)	3 (10)	3 (10)	4 (14)	13 (45)	0 (0)	8 ± 2
Receiving alerts with treatment changes is: *1. Not very useful ☹ 10. Very useful ☺*	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)	1 (4)	0 (0)	3 (10)	23 (79)	0 (0)	9 ± 1
Receiving reminds in my mobile of when to take my medication is: *1. Annoying ☹ 10. Helpful ☺*	0 (0)	0 (0)	1 (4)	0 (0)	1 (4)	3 (10)	1 (4)	0 (0)	4 (14)	18 (62)	1 (4)	9 ± 2
The questionnaires on adherence and attitude to therapy are: *1. Annoying ☹ 10. Appropriate ☺*	0 (0)	0 (0)	1 (4)	1 (4)	1 (4)	3 (10)	4 (14)	6 (21)	1 (4)	12 (41)	0 (0)	8 ± 2
The platform's Communication Module to contact my health professional is: *1. Difficult to use ☹ 10. Easy to use ☺*	0 (0)	0 (0)	0 (0)	0 (0)	2 (7)	1 (4)	1 (4)	3 (10)	1 (4)	(21) 72	0 (0)	9 ± 2
Having the platform's chat to resolve doubts with my pharmacist is: *1. Not very useful ☹ 10. Very useful ☺*	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)	0 (0)	2 (7)	1 (4)	2 (7)	23 (79)	0 (0)	10 ± 1

PUBLICATIONS

PUBLICATIONS

The studies which form this thesis work have been published or submitted to international journals as follows:

STUDY 1

Multimorbidity and medication complexity: New challenges in heart transplantation

M. Gomis-Pastor, E. Roig Minguell, S. Mirabet Perez, V. Brossa Loidi, L. Lopez Lopez, A. Diaz Bassons, A. Aretio Pousa, A. Feliu Ribera, A. Ferrero-Gregori, L. Guirado Perich, M. Mangues Bafalluy. Multimorbidity and medication complexity: New challenges in heart transplantation. Clin. Transplant. (2019) 0–3. DOI:10.1111/ctr.13682.

STUDY 2

Interdisciplinary mobile health model to improve therapy management and clinical care after heart transplantation: An implementation strategy study

Mar Gomis-Pastor, Esther Rodriguez-Murphy, Anna Feliu, Anna Barata, Gerardo Ontiveros, Francesc Garcia-Cuyàs, Albert Salazar, Sonia Mirabet, Vicens Brossa, Laura Lopez, Eulàlia Roig, M. Antònia Mangues. An interdisciplinary mobile health model to improve therapy management and clinical care after heart transplantation: An Implementation strategy study. Submitted. Pending acceptance.

STUDY 3

The mHeart mobile app to detect medication nonadherence in the heart transplant population: Validation study

Mar Gomis-Pastor, Eulàlia Roig, Sonia Mirabet, Jan T De Pourcq, Irene Conejo, Anna Feliu, Vicens Brossa, Laura Lopez, Andreu Ferrero-Gregori, Anna Barata, M. Antònia Mangues. The mHeart mobile app to detect medication nonadherence in the heart transplant population: Validation study. JMIR Mhealth Uhealth. 2020;8(2):e15957. DOI 10.2196/15957

STUDY 4

Improving patients' experience and medication adherence after heart transplant using a multilevel mHealth intervention: The mHeart randomized clinical trial

Mar Gomis-Pastor, Sonia Mirabet Perez, Eulàlia Roig Minguell, Nuria Mas, Vicenç Brossa Loidi, Laura López Lopez, M. Antònia Mangues Bafalluy. Improving patients' experience and medication adherence after heart transplant using a multilevel mHealth intervention: The mHeart randomized clinical trial. Submitted. Pending acceptance.

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- M. Gomis-Pastor, D. Gil, L. Lopez, V. Brossa, S. Mirabet, E. Roig, M. Mangues. Impact of mHealth in Heart Transplant Management (mHeart), Int. J. Integr. Care. 16 (2016) 38. doi:10.5334/ijic.2981.

- M. Gomis-Pastor, S. Mirabet, M. Mangues, E. Rodríguez-Murphy, J. De Pourcq, A. Feliu, A. Aretio, A. Ferrero, V. Brossa, L. Lopez, E. Roig. Impact of Mobile Health in Heart Transplant Management: The mHeart Study, J. Hear. Lung Transplant. 38 (2019) S273–S274. doi:10.1016/j.healun.2019.01.681.

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ORIGINAL ARTICLE

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Multimorbidity and medication complexity: New challenges in heart transplantation

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Abstract

Introduction: Multimorbidity and therapeutic complexity are a recognized problem in the heart transplant (HTx) population. However, little is known about how best to quantify this complexity or the strategies that could reduce its burden.

Methods: This single-center, observational study included adult heart transplant recipients (HTxR) >1.5 years from transplant. We assessed multimorbidity (>2 comorbidities) and the patient-level Medication Regimen Complexity Index Spanish version (pMRCI-S) score. We also analyzed the independent predictors of pMRCI-S and the impact of the index score on specific clinical variables.

Results: We included 135 chronic-stage HTxR. Comorbidities significantly increased after HTx (6 ± 3 vs 2 ± 2, *P*-value < .001). Patients took 12 ± 3 chronic drugs/d, 58% of them to treat comorbidities. The mean *total pMRCI-S score* was 42 ± 11, higher than in several other chronic diseases. The medication category *drugs to treat comorbidities* predicted a higher *total pMRCI-S score* (OR = 3.12, 95% CI 2.8-3.43, *P*-value < .001). Therapeutic complexity after HTx had an impact on solid malignancies (OR = 1.1, 95% CI 1.02-1.18, *P*-value = .02) and renal function (OR=−0.81, 95% CI −1.21-(−0.42), *P*-value < .001).

Conclusions: The multimorbidity and pMRCI-S scores obtained in HTx population were worrisomely high. The pMRCI score is a sensitive method that allows identification of the factors determining therapeutic complexity after HTx and selection of strategies to reduce pMRCI-S values.

KEYWORDS

comorbidity, heart transplantation, immunosuppression, interdisciplinary health team, long-term care, medication therapy management, multiple chronic conditions, polypharmacy, therapeutic index, treatment outcome

Eulalia Roig Mingell and Sonia Mirabet Perez contributed equally to this work.

[Corrections added on September 20, 2019, after first online publication: 2nd Affiliation changed from"Autonomous University of Barcelona (UAB),Barcelona, Spain" to "UAB Medicine Department, Autonomous University of Barcelona (UAB), Barcelona, Catalonia, Spain" .]

Original Paper

A Mobile App (mHeart) to Detect Medication Nonadherence in the Heart Transplant Population: Validation Study

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Abstract

Background: Medication nonadherence in heart transplant recipients (HTxR) is related to graft loss and death. mHeart is a mobile app that uses electronic patient-reported outcome measures (ePROMs) to identify and manage medication nonadherence in the outpatient heart transplant (HTx) population.

Objective: The study primarily aimed to validate mHeart to measure medication nonadherence in early stage HTxR by assessing the psychometric properties of ePROMs. The secondary aims were to (1) measure patient satisfaction with the mHeart tool and its usability and (2) explore the impact of a theory-based treatment on medication nonadherence rates to determine its scalability to larger research.

Methods: A prospective study was conducted in the outpatient clinic of a tertiary hospital. All consecutive early stage HTxR (<1.5 years from HTx) were included. The ePROM psychometric properties assessed were validity, reliability, responsiveness, interpretability, and burden. ePROMs comprised the 4-item Morisky-Green-Levine questionnaire and an adapted version of the Haynes-Sackett questionnaire. The Simplified Medication Adherence Questionnaire (SMAQ) was also applied on-site. Three consecutive medication nonadherence assessments were performed by a transplant pharmacist. To improve medication nonadherence, theory-based interventions were delivered in a 1-month period. Patient satisfaction was assessed by a semiquantitative Web-based survey at the end of the study.

Results: We included 31 early stage HTxR (age: mean 54 years, SD 12 years), and 71% (22/31) of them were men. The HTxR were taking a mean 13 (SD 4; range 7-18) drugs per day. A total of 42% (13/31) of patients were unaware of the consequences of medication nonadherence, and 39% (12/31) of patients were nonadherent to immunosuppressive treatment. The content validity measure showed excellent levels of expert panel agreement for the Haynes-Sacket (14/14, 100%) and Morisky-Green-Levine (13/14, 93%) questionnaires. SMAQ and Morisky-Green-Levine ePROMs showed similar measurement domains (convergent validity, phi=0.6, P<.001), which, as expected, differed from Haynes-Sackett ePROMs (divergent validity, phi=0.3, P=.12). Reliability assessment revealed a very strong association between ePROM and on-site PROMs (phi>0.7, P<.001). Reproducibility was moderate (Haynes-Sackett κ=0.6, P<.002) or poor (Morisky-Green-Levine κ=0.3, P=.11) because of unexpected improved medication adherence rates during the test-retest period. According to responsiveness, the theory-based multifaceted intervention

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POSTER ABSTRACT

Impact of mHealth in Heart Transplant Management (mHeart).

16th International Conference on Integrated Care, Barcelona 23-25 May 2016

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Introduction: Non-adherence to immunosuppressive medications following organ transplant ranges from 20-40% and is associated with episodes of acute rejection and graft loss. Focused on improving outcomes and safety associated with drug therapy, many solid organ transplant centres incorporate transplant pharmacists into the multidisciplinary transplant clinical team.

To improve patient empowerment and adherence to treatment, pharmacist and other clinicians seek new tools such as mobile Health (mHealth). Mobile technology has undergone rapid advances in recent years and could help manage chronic patients remotely. Several mobile applications have been designed to improve adherence but evidence supporting their benefits in clinical practice is limited.

We have designed a new pharmaceutical care programme supported by mobile health (mHealth) for use in heart transplant recipients. This study aims to analyse the potential of mHealth to improve adherence to medication following heart transplant in real clinical practice. The secondary objectives are to validate a new mHealth application and to evaluate drug-related problems and clinical events, practical barriers to adherence, patient quality of life and satisfaction, and reductions in healthcare costs.

Methods: We are performing a single-centre, interventional, parallel two- arm, open-label, randomized study.

The inclusion criteria are: heart transplant patients of either gender ≥ 18 years and at least 18 months post-transplant; and mobile device users. All patients gave informed consent and the intervention group signed a confidentiality agreement.

We will need to include 136 patients to achieve an improvement of 25% in adherence to immunosuppression treatment.

Medication adherence will be measured using immunosuppressive blood levels and data from clinical interviews, validated adherence scales, dispensing medication rates and self-reported mHealth medication. Using validated scales, we will measure stress, anxiety, depression, interpersonal support, use of the new technologies, and quality of life and satisfaction with the programme.

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5009-4 - NUEVAS ESTRATEGIAS PARA EL SEGUIMIENTO DE PACIENTES TRASPLANTADOS CARDIACOS: PROYECTO MHEART

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Resumen

Introducción y objetivos: El proyecto mHeart es un programa asistencial de atención farmacoterapéutica al paciente trasplantado cardiaco (TxC) con el soporte de las nuevas tecnologías. El objetivo principal es mejorar la adherencia al tratamiento debido al elevado impacto de esta en la supervivencia postrasplante.

Métodos: Estudio llevado a cabo en un hospital universitario terciario. Se llevó a cabo una selección de estrategias que combinadas pudieran mejorar la ruta asistencial actual: 1. Asistencia integral; 2. Nuevas tecnologías sanitarias; 3. Intervenciones efectivas y sostenibles (EMI). Fases del proyecto: 1. Estudio DIPP-mHeart. Desarrollo e implementación de una herramienta mHealth para el seguimiento del paciente crónico polimedicado adaptado al paciente TxC. 2014-2016. 2. Estudio Val-mHeart. Validación de mHeart como dispositivo médico. Pilotaje de 2 meses, 32 pacientes TxC, 2016. 3. Ensayo clínico mHeart (Clinicaltrials.gov NCT02554578). Medir el impacto del programa en rechazo, QoL y otras variables. 2 años, 136 pacientes TxC. Finalizó 31/01/2018.

Resultados: El estudio DIPP-mHeart dio lugar a la plataforma mHeart, página web y aplicación móvil para llevar a cabo un tratamiento integral de paciente con comorbilidades y polimedicado (figura). Una encuesta a profesionales y pacientes nos permitió conocer potenciales limitaciones que debían ser resueltas: 1. Calidad y seguridad; 2. Integración; 3. Implementación, extensibilidad y coste; 4. Protección de datos confidenciales; 5. Inversión de tiempo de profesionales. La plataforma se encuentra integrada en el entorno sanitario monitorizada por 1 enfermera, 1 farmacéutica y 1 psicóloga. El estudio piloto Val-mHeart, confirmó que mediante la plataforma mHeart se podían identificar pacientes no adherentes y mejorar > 25% la adherencia al tratamiento (test Hayness-Sacket y Morisky-Green) en pacientes polimedicados TxC. Además de obtener una elevada satisfacción en los pacientes, el 100% de los cuales recomendarían su uso a otro paciente. El ensayo clínico mHeart se encuentra en fase de análisis.

Aplicación móvil mHeart de seguimiento integral del paciente trasplantado cardiaco.

Conclusiones: Se ha obtenido una plataforma de soporte asistencial al seguimiento integral del paciente crónico polimedicado fácilmente adaptable a las necesidades de otras unidades de cardiología. La plataforma mHeart ha demostrado mejorar la adherencia terapéutica en pacientes trasplantados cardiacos con un elevado grado de satisfacción.

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Effect of Donor Simvastatin Treatment on Cardiac Allograft Ischemia-Reperfusion Injury (IRI) - 1-Year Follow-Up Analysis of a Randomized Prospective Single-Center Clinical Trial

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Purpose: Cardiac allograft IRI may lead to deleterious short- and long-term effects. Experimental studies show that donor statin treatment protects heart allograft from both IRI and chronic allograft vasculopathy. Here, we analyzed the 1-year follow-up data on the effect of donor simvastatin treatment on cardiac allograft.

Methods: We randomized 84 heart transplant donors to a control group, or to receive simvastatin 80mg at the time of graft acceptance in a single-center clinical trial. IRI was evaluated by cardiac enzyme release. Patient survival, biopsy-proven rejections, intravenous rejection treatments and postoperative proBNP levels have been currently followed up to 1 year.

Results: Plasma TnT and TnI values peaked at 6 hours. Donor simvastatin treatment decreased plasma troponin T and I (by 34% and 40%, respectively; both P<0.05) levels 6 hours after reperfusion. Donor simvastatin also decreased proBNP (by 37%; P<0.05) at 1 week after transplantation, and the need for intravenous rejection treatments (by 53%; P<0.05) in the first postoperative month. At 1-year, proBNP levels (2400 vs 3400 ng/L; P=ns) and mortality (93% vs 86%; P=ns) remained slightly lower in the donor simvastatin treatment arm compared to control group. Also the need for intravenous rejection treatments (33 vs 16; P=ns) and the number of biopsy-proven rejections (69 vs 48; P=ns) were lower in the donor simvastatin group.

Conclusion: Donor simvastatin treatment decreased early postoperative IRI and improved early graft function as measured by plasma troponin and proBNP levels. It also reduced the need for early rejection treatments. In a 1-year follow-up, these differences can still be seen, but the difference between groups has evened to statistically non-significant.

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Clinical Outcomes of Perioperative Desensitization in Orthotopic Heart Transplant Recipients

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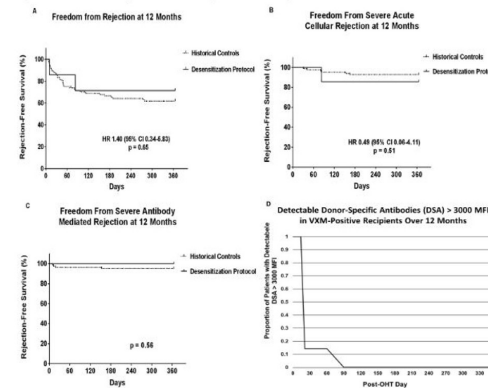
Purpose: Transplantation of sensitized recipients is associated with suboptimal post-transplant outcomes. This study assessed the effects of a perioperative desensitization strategy in virtual crossmatch (VXM)-positive orthotopic heart transplant (OHT) recipients compared to a historical cohort of VXM-negative OHT recipients.

Methods: This single-center, retrospective study included OHT recipients from 2010-2018. VXM-positive patients received perioperative plasmapheresis, intravenous immunoglobulin (IVIg), and antithymocyte globulin (rATG). VXM-negative historical controls received either high-dose steroids or alemtuzumab induction. Maintenance immunosuppression consisted of tacrolimus, mycophenolate, and a steroid taper. The primary endpoint was graft survival at 12 months. Secondary endpoints included freedom from acute rejection and freedom from severe (i.e., grade $\geq$ 2) acute cellular rejection or antibody-mediated rejection at 12 months.

Results: Of 91 patients included, 7 received desensitization. Baseline demographics, disease etiology, and comorbid conditions were similar between groups. VXM-positive recipients received a median of 5.1 (4.8-5.3) mg/kg of rATG, 0.9 (0-1.2) g/kg of IVIg, and 6 (3-7) plasmapheresis sessions. Maintenance immunosuppression was similar at all time points. There was one graft loss, which occurred in the VXM-negative cohort at 70 days post-OHT. The median time to rejection was 44.5 (16.5-93.5) days in the VXM-negative group versus 46.5 (10-83) days in the VXM-positive group (p=0.76). There were no differences in any other rejection outcomes. Six VXM-positive recipients cleared donor-specific antibodies (DSA) by day 21 and all cleared DSA by day 60 (Figure 1).

Conclusion: These data suggest that transplantation of VXM-positive OHT recipients receiving perioperative desensitization is feasible without excess graft loss or acute rejection at 12 months. The rapid clearance and lack of DSA recurrence is promising for long-term outcomes.

Figure 1. Survival Analyses and Donor-Specific Antibody Clearance



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Impact of Mobile Health in Heart Transplant Management: The mHeart Study

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Purpose: Non-adherence to immunosuppressive medications following organ transplant ranges from 20-40% and is associated with episodes of acute rejection and graft loss. This would justify implementing multidisciplinary interventions designed to improve therapy management but also patient empowerment. New tools such as mobile Health (mHealth) could help manage chronic patients remotely.

The aim of this study is to measure the therapeutical adherence (TA) improvement by means of a personalized care programme in a multidisciplinary environment, together with the support of Mobile Health Technology (mHealth) following heart transplant (HTx).

Methods: A prospective pilot study was carried out in a third-level hospital. Patients who had received a HTx in the past 18 months and had a mobile device were included. TA was assessed by the SMAQ validated test at the beginning and end of the two-months follow-up. Personalized interventions on-line via the mHeart platform were performed with the aim to improve TA. The mHeart platform is a mobile application and a website directed to facilitate communication with the patient and to record timing of medication intake, drug-interactions, vital signs, side effects and symptoms.

An independent statistician analysed the data (IBM-SPSS V22.0).

Results: Of the 35 eligible recipients, 32 (91.4%) were included in the study; 23 (71.9%) were men of an average age of 52.4 years [42.9-63.7] taking a median of 12 [8.5-14] different daily drugs. The follow-up time was 2.03 months [1.3-2.5].

The effectiveness of the pharmaceutical interventions implemented through the mHeart tool was high: 83% of the nonadherent recipients in the first visit became adherent at the end of the study according to the SMAQ test.

C398.5

Effects of Transcutaneous Nerve Stimulation on the Autonomic Balance of Cardiac Transplant Recipients

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Introduction: Patients submitted to cardiac transplant surgery present an increase in resting heart rate. This fact is related to the reduction of direct autonomic control over the organ that, when implanted, is denervated, with reduced heart rate variability (HRV). Electrical stimulation in PC5 and PC6 acupuncture points has been described as possible complementary therapy capable of increasing heart rate variability in healthy individuals with cardiovascular diseases.
Objective: The aim of this study was to analyze the acute effect of transcutaneous electrostimulation in acupuncture points (TEAS) at points PC5 and PC6 on the autonomic balance in cardiac transplant recipients and to analyze the risks that the procedure offers.
Methods: This pilot study is an uncontrolled clinical trial. Cardiac transplant patients older than 18 years were recruited on outpatient follow-up at a cardiology hospital. The experiment started with the monitoring through the heart rate monitor that recorded the RR intervals. The patient remained lying down for 20 min for accommodation, 40 min for TEAS application with Jianshi (PC5) and Neiguan (PC6) electrodes in forearm region and 20 min for recovery. The indices in the time and frequency domains were considered for study. It was observed if there was an adverse effect during the protocol and in the subsequent 48 hours through telephone contact, such as dizziness, nausea, vomiting, hemodynamic instability.
Results and Discussion: SDNN increased ($P < 0.05$) during TEAS and recovery. The very low frequency (VLF), low frequency (LF) and high frequency (HF) indices were not altered by TEAS. However, the simpatovagal index increased during TEAS in relation to the accommodation period ($P < 0.001$). Both the diastolic pressure variation and the mean arterial pressure were higher ($P < 0.01$) in the recovery period when compared to the accommodation. There was also a moderate correlation ($r = 0.52$, $P < 0.05$) between the sympathovagal index and the effect of TEAS on heart rate. There was also a correlation between the time after surgery and the effect of TEAS on the variation of sistolic bloop pressue ($r = 0.51$, $P = 0.016$) and double product ($r = 0.47$, $P < 0.05$). No adverse effects were identified during the experimental protocol or in the 48 hours following the protocol.
Conclusion: The results suggest that TEAS modulates the autonomic balance of cardiac transplant patients submitted to TEAS and has been shown to be a safe practice for these patients.

Keywords: Transcutaneous electrical nerve stimulation; Acupuncture points; Autonomic nervous system; Heart transplantation.

C398.6

Impact of a Mobile Pharmaceutical and Healthcare Programme on Therapeutical Adherence in Heart Transplant P atients

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Background and Objectives: Low therapeutical adherence (TA) to immunosuppressive drugs is one of the main factors that determine the survival of Heart Transplant (HT) patients. The aim of this study is to improve the TA of HT patients by means of a personalised care programme in a multidisciplinary environment, together with the support of mHeart platform.
Materials and Methods: The mHeart platform is a healthcare tool designed to improve TA and consists of an App and a support web page. Currently, it is under a clinical trial (ID mHeart NCT02554578). This tool allows the patient to record timing of medication intake, complementary therapy, vital signs, side effects and symptoms, as well as facilitating communication with the multidisciplinary team.

A prospective two-month study was carried out in a third-level hospital. All patients that had access to a mobile device and who had received CT in the past 18 months were included in the mHeart clinical trial. Personalised interventions both on-site and on-line via the mHeart platform, were performed with a view to improving TA. TA was assessed by means of validated tests applied during on-site visits scheduled at the beginning and end of the study (Haynes-Sackett y Morisky-Green). An independent statistician analysed the statistics using the IBM-SPSS (V22.0) Statistics pack.
Results: Of the 35 patients (p) considered for inclusion, 32p (91.4%) were included in the study; 23p (71.9%) were men of an average age of 52.4 [42.9-63.7]. The follow-up time was 2.03 months [1.3-2.5].

With regard to polypharmacy, a median of 12 [8.5-14] different daily drugs was obtained, with 15 drugs being used in the case of 7p (22%). Other factors associated with lower TA were: patients' perception of taking too many drugs (17p) and patients feeling that taking their medication was highly inconvenient [4p (12.6%)] ;>8/10]. In relation to patients' choosing where to take their prescriptions, 27p (84.4%) stated that they regularly collected them from the same drugstore.

TA during the first and last visit was 71.4%-89.3% according to the Haynes-Sackett TA test and 67.9%-85,71% for Morisky-Green. In both cases, TA increases more than 17% ($p>0.05$). In both tests the final TA figure was over 85%, the target figure in solid organ transplants.

With reference to the effectiveness of the pharmaceutical interventions, 6 to 8 patients (75%) who were nonadherent in the first visit, were adherent in the final visit according to Haynes-Sackett and 7 out of 9p (78%) in compliance with Morisky-Green. In both cases, >75% of the patients became adherent during the follow-up time.
Conclusions: Obtaining information on how patients included in this study perceived the burden and inconvenience related to their medication, made the identification of patients at risk of low therapeutic adherence easier. The programme that was set up permits effective supervision of nonadherent patients, resulting in a clinically significant improvement in TA.

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