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STUDY PROTOCOL

# Protocol for Surveying Participants and Professionals' Experiences in an International Kidney Transplant Clinical Trial

[version 1; peer review: 1 approved with reservations]

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## Abstract

### Background

Therapeutic misconception is a phenomenon in which participants or researchers misunderstand the nature and purpose of a clinical trial, believing that the primary goal of the trial is to provide them with individualized therapeutic benefit rather than to generate generalizable knowledge that will benefit future patients. Therefore, the perspectives of participants and researchers on these issues are central to improving the quality of health research to increase participant awareness and avoid therapeutic misconceptions.

### Objective

The main objective of this study is to explore the views and experiences of patients and healthcare professionals regarding their participation in a clinical trial, the TTVguideIT randomized controlled trial, as part of the EU funded TTVguideTX project. The study was designed to identify therapeutic misconceptions of participants and health care professionals, assess their experiences with the informed consent process and their concerns regarding privacy and data protection.

**Open Peer Review**

**Approval Status** ?

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1. **Chiara Crico**, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy

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**Methods**

This study is based on two distinct questionnaires, one intended for the professionals involved in the TTVguideIT clinical trial and the other for the patients. The questionnaires can be completed both online and on paper, allowing each individual to choose the format that suits them best. The questionnaires are written in the languages of the six participating countries, namely German, Spanish, French, Dutch, and Czech.

**Conclusion**

This study may help future research design and implementation to include participants' and professionals perspectives on the informed consent process and privacy and data protection, and aspects aimed at minimizing therapeutic misconceptions.

**Plain language summary**

Sometimes, people involved in clinical trials think the main goal is to provide them with personal medical benefits. However, the real aim is to gather knowledge that can help future patients. Understanding the views of both participants and researchers can help improve how clinical trials are conducted and ensure everyone understands the true purpose. This study looks at what patients and healthcare professionals think about their involvement in a specific clinical trial called TTVguideIT. It aims to find out if they have any misunderstandings about the trial's purpose, how they feel about the informed consent process, and their concerns about privacy and data protection. The TTVguideIT trial is part of a larger EU-funded project. It's a carefully controlled study involving patients and healthcare professionals from six European countries. As part of it, participants are asked to fill out a questionnaire, either on paper or online, in their preferred language (Czech, Dutch, French, German or Spanish). The findings from this study could help improve future clinical trials by incorporating participants' views on informed consent and privacy, and by reducing misunderstandings about the trial's purpose.

**Keywords**

Clinical trial, Therapeutic misconception, Informed consent, Patient Data Privacy, Knowledge, Attitudes

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## Background

Clinical research aims to increase our understanding of human health and illness, as well as evaluate approaches for prevention, diagnosis, treatment, and patient care. Clinical research encompasses pre-clinical studies in laboratories and animals, followed by clinical trials to assess the safety and efficacy of therapies in humans. Clinical trials are the most reliable method to establish the safety and effectiveness of treatment or preventive measures for diseases.

Nurses play a crucial role in conducting ethical clinical research, facing complex clinical, ethical, and legal challenges[1]. As clinical research becomes more diverse and complicated, nurses face greater challenges in conducting ethical research. Understanding and addressing the ethical issues nurses face in clinical research is critical to maintaining their moral commitment to patient rights and safety[2]. When nurses are involved in research (as principal investigators, study coordinators, clinical trial nurses, and staff nurses), they have a responsibility to promote ethical research practices. To promote needed clinical research while protecting the rights of individuals, it's important to understand the differences between clinical research and clinical practice. If researcher clinicians, including nurses, do not understand the purpose of the study or the importance of informed consent in research, they may not be able to help their patients, as potential clinical trial participants, make an informed decision[2].

Clinical research and clinical care have different goals and approaches, which can be a source of tension among nurses and other healthcare workers[2]. Clinical care involves efforts that prioritize a patient's well-being and medical needs based on the specific situation at hand. Clinical research aims to answer questions and develop information for the benefit of patients and society. Research often aims to assess the safety and effectiveness of interventions for certain illnesses. While some research may give medical benefits to participants, this is not the primary purpose. In clinical research, requiring individual subjects to accept research burdens and risks for the benefit of others leads to ethical tension and responsibility. These ethical requirements include scientific rigor, social accountability, and respect for individual participants' rights and welfare. Nurses, doctors, and other healthcare professionals have an ethical responsibility to promote good science while also protecting patient rights and welfare.

Clinical research poses various specific ethical issues. One of the key ethical concerns found in previous studies is that research participants can confuse medical research with ordinary medical care, which is known as "therapeutic misconception"[3]. A therapeutic misconception is closely related to the difficulty of understanding the differences between participation in a trial and the medical care that participants receive when enrolled in a biomedical trial. When participants in clinical research assume that the goal of clinical research is always therapeutic and when they do not understand, for example, that they may be randomly assigned to a study condition that is not in their best personal interest, a therapeutic misconception occurs. This misconception is even more likely to happen when the study researcher is someone whom participants know and trust as a treatment provider and who is asking them if they would like to participate in a research study[4]. Various studies have attempted to explain why therapeutic misconceptions occur, while others have examined the role of researchers in their formation[5,6].

In addition to therapeutic misconceptions, there are other ethical challenges, such as the importance of privacy in research from the perspective of the participants. It has been noted that patients want to be involved in the development and evaluation of new treatments and are eager to share their thoughts and opinions through participatory design procedures, which can significantly shorten recruitment periods and help bring innovative medicines to market faster[7]. Previous research has found that motivations, understanding and voluntariness to participate in international randomized trials vary and depend on several factors, such as disease and other demographic factors[7–10]. A recent systematic review identified 23 original research articles on the perceptions or attitudes of patients and patient family members or the general public toward clinical research participation in the Eastern Mediterranean region[11]. The most commonly reported motivators were a personal benefit to the individual, altruism and desire to help others, the research process, medical influence, family encouragement, and religion. Concerns about confidentiality and other variables beyond the study process include a lack of trust in healthcare professionals or the healthcare system, a lack of interest in research, and religion. The most commonly reported barriers to participation were lack of research interest and anticipated personal benefit, religious concerns, and family/cultural considerations.

On the one hand, understanding participants' experiences in a clinical trial is crucial for several reasons. First, by understanding their experiences, researchers can identify any issues or concerns that may arise during the trial and address them promptly. In addition, participants' experiences can provide insights into the quality of care they receive during the trial. This includes aspects such as communication with researchers, access to information, and the overall environment of the trial site. Understanding their experiences allows researchers to consider their needs, preferences, and priorities, ultimately leading to more relevant and meaningful research outcomes. On the other hand, understanding the experiences of clinician-researchers in a clinical trial is equally important for several reasons. Clinician-researchers are responsible for implementing the study protocol and administering interventions to participants. Understanding their experiences can provide valuable insights into the potential ethical challenges encountered during implementation, and it can also help to identify training and support needs. Understanding their experiences can highlight areas where additional training or support interventions are needed, such as therapeutic misconception, or guidance on handling participant interactions.

Insights gained from clinician-researchers' experiences can inform the ethical optimization of research processes and procedures to enhance the overall conduct of the trial.

Thus, to understand the participants and researchers' experiences regarding ethical, legal, and social aspects of a clinical trial, we present here the study protocol for a survey with a dual aim. First, one goal of this study is to explore the perspectives and experiences of patients in a randomized controlled trial, with a focus on the ethical aspects. In addition, the other goal is to explore the views and opinions about the same ethical aspects of healthcare professionals involved in the trial, including nephrologists, nurses, virologists, laboratory staff, etc.

This study will be conducted as part of the TTV GUIDE TX project, which aims to optimize immunosuppressive drugs in kidney transplant recipients (TTVguideIT) and to identify therapeutic misconceptions in both groups and their concerns about consent, privacy and data protection. The TTVguideTX project is an EU-funded project that aims to create a tool for quantifying the immune system. Within a randomized controlled trial (TTVguideIT) the project tests the safety and efficacy of personalization of immunosuppression in kidney transplant based on Torque Teno virus (TTV) load in the blood. TTV[1] can be detected in every adult, it does not cause disease and its copy number in the blood is associated with its host's immune function. In kidney transplant recipients a low TTV load indicates a strong immune system and low immunosuppression and thus risk of organ rejection. A high TTV load indicates high immunosuppression and thus risk for infection. Quantifying the TTV viral load in the blood of kidney transplant recipients may help optimizing the dosage of immunosuppressive drugs to reduce infections and rejections as consequence of intense and insufficient immunosuppression, respectively. The TTVguideIT trial tests TTV-guided dosing of immunosuppressive drugs in a randomized controlled trial involving 264 kidney transplant recipients from across Europe.

To analyze the participants' and researchers' perspectives on the information process, voluntariness, and privacy in clinical research is crucial to improve the communication process in clinical trials recruitment. Such findings can provide valuable information for improving the quality of health research.

## Methods

### Primary goal

- To gather information on participants' and clinical staff's (nephrologists, nurses, virologists, laboratory staff, etc) experiences, opinions, and attitudes regarding ethical, legal, and social aspects of the clinical trial TTVguideIT

### Secondary goals

- To explore patient motivations for enrolling in the clinical trial.
- To explore healthcare professionals' motivation to collaborate in the clinical trial.
- To identify instances of therapeutic misconception in both groups, participants and clinicians;
- To assess participants' and professionals' attitudes and experience towards informed consent in the clinical trial;
- To identify concerns about data protection in clinical trials from the perspective of healthcare professionals and patients.

### Design

Two questionnaires have been designed for the ELSI study, as part of the TTVguideIT trial. The trial protocol has been published in detail elsewhere[12]. In short, kidney transplant recipients are randomized in a 1:1 ratio to receive either standard or TTV-guided immunosuppression. The primary end-point is a compound of death, graft loss, transplant rejection and infection. The ELSI study consist of questionnaires that can be fulfilled both online or in a printed copy. The questionnaires gather information on participants' and clinical staff's experience, opinions and attitudes regarding ethical, legal and social aspects of the TTVguideIT trial. The study does not collect any relevant data for clinical safety endpoints of the clinical trial.

### Study population

The target population for this study is, on the one hand, the patients who participate in the TTVguideIT trial; and on the other hand, the healthcare professional staff involved in the clinical trial (nurses, physicians, virologists, technicians, students, etc.). There are no exclusion criteria. The sample covers the entire population. An estimated number of participants is shown in Table 1.

### Study settings

The TTVguideIT trial is conducted in 6 European countries, as shown in Table 1. In these countries, the trial is conducted at a total of 13 clinical centers, so the survey is administered at these centers (Table 1).

### Recruitment process

Adult recipients of a kidney are invited to participate in the TTVguideIT trial within the first two weeks following transplantation. Patients who give their written informed consent to participate will first be enrolled in a screening phase of the study. Following the completion of this phase, if all inclusion criteria are met and no exclusion criteria are present, they will be enrolled in the clinical trial and randomised at the end of the fourth month after transplantation (Visit 1). Participants will then attend an outpatient clinic every six weeks, up to and

[1] Abbreviations: ELSI: Ethical, legal, and social implications; GDPR: General Data Protection Requirement; TTV: Torque Teno virus

**Table 1. Centres involved in the TTVguideIT trial and estimated participants.**

| Country | Center | Former Recruitment Target (TTVguideIT) |
|---|---|---|
| Austria | Medical University of Vienna | 44 |
| | Medizinische Universität Innsbruck | 22 |
| | Medizinische Universität Graz | 12 |
| | Ordensklinikum Linz | 12 |
| Czech Republic | Institute of Clinical and Experimental Medicine (IKEM) | 15 |
| France | CHU Grenoble Alpes | 12 |
| | Les Hôpitaux Universitaires de Strasbourg | 10 |
| Germany | Technische Universität Dresden | 28 |
| | Universitätsklinikum Regensburg | 12 |
| | CHARITE Universitätsmedizin Berlin | 12 |
| Spain | Hospital La Fe Valencia | 12 |
| The Netherlands | Leiden University Medical Center | 30 |
| | UMCG Groningen | 39 |
| | Total | 260 |

including month 12 after transplantation (Visit 2–Visit 6). Follow-up will be performed until month 13 post-transplantation (V7).

Patients: Once enrolled in the TTVguideIT trial, participants are invited to participate in the ELSI Study during the Visit 2. Once we have obtained their written informed consent, participants are invited to complete the questionnaire. The information sheet and the questionnaire (see extended data) will be distributed simultaneously, and the participants can decide whether they prefer to fill out the survey online (by clicking a QR code) or fill out the printed copy and return it on the following visit.

Healthcare professionals: The trial coordinator at each site will distribute the information sheet and the questionnaire to healthcare professionals (see extended data). After we have obtained their written informed consent, healthcare professionals are invited to complete the questionnaire. Each person can complete the quetsionnaire only once. However, there will be at least two cut-off points to collect their responses in case some are absent during the first call for participation. To ensure an equal period of participation in the study across all study sites, participation will be offered 6 months after the start of the clinical trial or alternatively one year after the start of the clinical trial. Like patients, they can choose to complete the survey online or on paper.

The information sheet for both groups include the objectives and procedures of the study, risks and inconveniences (see extended data). Participants can decide if they prefer to access the survey online, or if they prefer to fill the printed copy. In the online platform, the authorization to participate is requested, and once the subjects authorize, the questionnaire begins. The survey is attached to the information sheet and the link to complete the survey online. Participants can decide if they prefer to access the survey online, or if they prefer to fill the printed copy. If they fill out the printed copy, they will return it to the coordinator of the trial in a sealed envelope that will be provided.

## Data collection

Data will be collected using online surveys or hardcopy versions that participants can return anonymously. A web platform will be made available to only participants and members of the research team, with a personal use code issued on the online platform. Participants give the needed sociodemographic information. The responses to the questions are fully anonymous. Each participant must submit their written responses to the coordinator in a sealed envelope. The trial organizer will collect sealed envelopes from patients and professionals. The trial coordinator will send it to the research coordinator of the ELSI study at the University of Granada.

The trial coordinator will bundle all of the envelopes containing responses from both patients and professionals and mail them to WP 2 at the University of Granada. Data will be collected using online surveys or printed copies that participants can return anonymously. Participants will provide the needed sociodemographic information. The responses to the questions are fully anonymous.

### Questionnaire development

The questionnaires address ethical, legal and social issues (ELSI) that arise in the context of clinical trials, and specifically explore the experience within the TTVguideIT trial (see extended data). The questionnaires (for both participants and professionals) consist of four sections: the first relates to the reasons/motivations why participants or professionals are involved in this clinical trial; the second relates to an assessment of the extent to which participants may have therapeutic misconceptions; the third relates to their experience of the informed consent process; and the fourth relates to their concerns about privacy. Finally, some demographic data (age range, gender) are collected. The research team decided to ask for the age range to minimize any remote possibility of re-identification. The research team involved patient representatives from the Spanish National Federation of Associations for the Fight against Kidney Diseases (ALCER) in the design of the questionnaire to ensure the readability and relevance of the topics addressed. Patient representatives reviewed the draft survey and provided feedback. In translating the questionnaires, the research team was supported by the clinical trial center representatives in each country.

Once the survey was translated from English into Czech, Dutch, French, German, and Spanish, the online survey was prepared using the Qualtrics platform. This platform ensures that the data is secure and compliant with ISO 27001 International Organization for Standardization; GDPR (EU's General Data Protection Requirement).

### Privacy and data protection

The research team will not receive or collect any personally identifiable information, such as name, date of birth, social security number, etc., only self-reported background information, such as age range and gender. Only authorized researchers on the study team will see the survey responses. Participants will use a code provided on the platform to access the survey. The code will be secured and the survey data will be stored at the University of Granada for a maximum of 8 years. In the case of paper documents, the research team will assign a numerical code to the documents as soon as they are received. When the study data are published, the information will be presented at the group level. Individuals will not be identified. The results of the study will be published in a peer-reviewed journal.

The information obtained either at the time of recruitment of panelists or at the time of responding to the survey questionnaires is protected by Law 12/89, which regulates the management of statistical data in Spain. To protect the anonymity of the respondents, none of this information can be processed or distributed other than in numerical and aggregated form. The University of Granada applies the appropriate security measures to comply with Organic Law 3/2018, of December 5, on the Protection of Personal Data and the Guarantee of Digital Rights. Following the General Data Protection Regulation 2016/679, of April 27th, approved by the European Parliament and the Council, if personal data is collected, you may exercise your rights of access, rectification, portability, cancellation and opposition at any time. However, as this questionnaire is anonymous - without reference to personal data - the GDPR does not apply.

### Ethics

The ELSI study adheres to the Declaration of Helsinki. The survey gathers data in an anonymous manner, devoid of any personal identifiers. Written informed consent is obtained from all participants, both patients and healthcare professionals. Ethics approval has been obtained from the Ethics Committee of the Institute for Clinical and Experimental Medicine and the Thomayer University Hospital in the Czech Republic (register number: 21106/22, A-22-23; date: 09/01/2022), and from the Ethics Committe of the Hospital Universitario y Politécnico La Fe, Valencia, Spain (register number: 2022-622-1; date: 07.20.2022). Following discussions with the local Institutional Review Boards in Austria, France, Germany, and The Netherlands, it was determined that neither an ethical evaluation nor the consultation of the local ethics committee was required. The trial was approved on 04.07.2022 via CTIS for all participating countries. Written informed consent to participate will be obtained from all participants.

## Dissemination

The results will be disseminated via publication in a peer-reviewed medical journal and may be presented at local, regional, national and international conferences.

## Limitations

Since our survey is administered as part of a clinical trial, a low participation rate is possible. Although the estimated time to complete the survey is approximately 10 minutes, some patients participating in the clinical trial may decline to participate in the survey precisely because they are already enrolled in the TTVguideIT trial. Participating in a second sub-study may take some time and they may not want to share more time. Similarly, healthcare professionals may not have enough time. In addition, some survey concepts are complex. Although we have shared the questionnaire with the research team in each country to review and clarify questions, some respondents may have difficulty understanding some of the questions to make a meaningful assessment.

## Conclusions

This ELSI study is innovative in several ways. First, it proposes to explore the therapeutic misconception not only in patients who participate in a clinical trial but also in healthcare professionals involved in the research. The findings can shed some light on what factors contribute mainly to this phenomenon. Second, to the best of our knowledge, no prior studies have explored how both patients and professionals who participate in the same clinical trial perceive the informed consent process they are involved in as part of said trial. By exploring both views, we might identify some discrepancies in the way in which participants and professionals perceive the transparency and clarity of the communication. This study may help future research design and implementation to include participants'

perspectives on the informed consent process, privacy and data protection concerns, and aspects aimed at avoiding therapeutic misconceptions. We hope that this protocol will encourage ethical nurses to further develop research to address how to improve the ethical, legal, and social aspects of patient participation in clinical trials, as well as the ethical performance of healthcare professionals. Nurses often have a unique perspective on health care delivery, patient care, and the health care system as a whole. As such, their frontline experience can provide valuable insights into patient needs and experiences that can inform the design and conduct of ethical research studies.

## Data availability

No data are associated with this article.

### Extended data

OSF: ELSI study - TTV guide TX: DOI 10.17605/OSF.IO/TPMVK

*This project contains the following underlying data:*

The information sheets and the questionnaires for patients and for professionals are available at the Open Science Framework repository: DOI 10.17605/OSF.IO/TPMVK

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# Open Peer Review

## Current Peer Review Status: ?

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Delgado et al. present the protocol of a study aimed at investigating the ethical, legal, and social aspects of clinical trials, integrating the perspectives of both patients and clinicians/researchers, with a particular focus on “therapeutic misconception” in clinical research. The study is embedded in a multicentre, European-funded randomized trial evaluating an innovative approach to immunosuppressant dosing in kidney transplant recipients (TTVguideIT trial).

Delgado and colleagues offer several innovative contributions, such as the inclusion of clinicians’ perspectives  rather than focusing exclusively on patients – and the exploration of highly relevant ethical issues such as therapeutic misconception. For these reasons, the article is of clear interest. However, several issues can be identified

Background

• The background section is overly long and general, at times confusing, and the intended target audience is not always clear. In the first paragraph, for example, the authors provide a very broad introduc1on to clinical trials that appears more educa1onal than problem-oriented, suggesting a style more suited to an inexperienced audience (e.g., patients or lay readers) rather than to a readership of clinical or academic researchers.

• The second paragraph focuses on the role of nurses, highlighting the ethical, legal, and social challenges they face in clinical trials, which seems to suggest that nurses are the primary focus of the study an impression not supported by the remainder of the manuscript. The authors do not clarify how the challenges faced by nurses differ from those experienced by other healthcare professionals involved in clinical research.

• The authors do they clearly define the challenges faced by healthcare professionals involved in clinical research in general. In the fourth paragraph, reference is made to “various ethical issues” in clinical research, yet only two are effec1vely discussed (namely, therapeutic misconcep1on and issues related to privacy and confiden1ality in the fifth paragraph), without sufficiently detailing

the later; in this regard, the authors mention “lack of trust” without better explaining this concept or clarifying how it relates to confidentiality.

• The rationale for focusing specifically on therapeutic misconception in kidney transplant recipients is also insufficiently developed. Although it is clear that the protocol is embedded within a study involving kidney transplant patients, the manuscript would benefit from a more explicit justifica1on of why therapeutic misconception is particularly relevant in this population. In par1cular, it would be important to clarify whether kidney transplant recipients present specific characteristics that may increase susceptibility to therapeutic misconception, distinguish them from other clinical populations, or expose them to a higher risk of misunderstanding or potentially more significant consequences.

Methods • Three of the secondary aims appear to be subcomponents of the primary aim rather than distinct research ques1ons.

• The reference to the TTVguideIT trial should be moved to the background section rather than the methods. The paragraph describing the recruitment process of the TTVguideIT trial is unnecessary and should be omitted, as a reference to the trial protocol would suffice; subsequent sections should be adjusted accordingly. • The two questionnaires are not included in the protocol, and it is therefore unclear what types of questions will be asked. In addition, there is no description of the planned analytical approach for the collected data (for instance, it is not specified how therapeu1c misconception will be assessed).

• In the second subparagraph of the “Privacy and data protection” sec1on, the authors refer to the “recruitment of panelists,” but it is unclear who these panelists are (this is the only men1on of panelist). Overall, the manuscript appears redundant in several parts. Some sections restate the same concepts multiple times in slightly different wording (e.g., within the Methods section, recruitment process and data collection), while certain details are unnecessarily repeated across different paragraphs (such as the possibility of completing ques1onnaires either online or on paper, depending on participant preference). There is also inclusion of nonessential information (for example, an extended explana1on of GDPR in the final subsection of “Privacy and data protection,” despite its limited relevance to the study context). A thorough rephrasing and streamlining of these sections are recommended.

**Is the rationale for, and objectives of, the study clearly described?**

Partly

**Is the study design appropriate for the research question?**

Partly

**Are sufficient details of the methods provided to allow replication by others?**

No

**Are the datasets clearly presented in a useable and accessible format?**

Not applicable

***Competing Interests:*** No competing interests were disclosed.

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.**