An Ethics and Governance Framework for the TTV GUIDE TX Project

April 2022

TTV GUIDE
Torque Teno Virus Based Immune Monitoring

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Disclaimer

This report proposes an ethical framework for the TTV GUIDE TX Project. This framework is intended to support and help ensure that the health research conducted within the TTV GUIDE TX project is ethically sound and provides guidance and a review process for research protocols and their refinement. The ethical framework had been discussed and developed by the authors/investigators.

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Executive Summary

This Ethical Framework is intended for use by any individual researcher, organization or institution within the TTV GUIDE TX project (Personalisation of Immunosuppression by Monitoring Viral Load Post Kidney Transplantation - A Randomised Controlled Phase II) and potential research participants. We set out the principles and values for good ethical conduct of research at TTV GUIDE TX project. This Ethical Framework will help those involved in the TTV GUIDE TX project to understand their responsibilities for research ethics and ethical review and monitoring of human research, and provides criteria for their accountability.

Purpose and Overview

This Ethical Framework adopts a consensual approach within professional bioethics, with agreed principles for assessing the value of responsible research practice. It is intended as a guide to both health professionals and participants in the TTV GUIDE TX Project, in situations of possible ethical and/or moral conflict. It is not based on a particular and overarching moral theory, but rather on medical ethics principles and human rights.

The main purpose of this document is to promote ethics research excellence. Satisfying this purpose implies that participants assert their rights to respect and protection, and that clinicians promote research guided by ethical principles. Consequently, this ethical framework is explicitly designed to clarify the ethical responsibilities of:

- Institutions and researchers involved in the TTV GUIDE TX for the design, conduct and dissemination of results of human research; and
- Review bodies and ethics committees.

This Ethical Framework also aims at clarifying the participants' doubts regarding the evaluation process and ethical assessment for clinical trials and scientific studies, and to inform the public as well. It should be used to shape the design, ethical review and conduct of human research that takes place under the auspices of the TTV GUIDE TX project. Therefore, this Ethical Framework sets the standards for good practice in clinical research for any individual, institution or organization involved in the TTV GUIDE TX project.

Background

TTV GUIDE TX project is an EU funded project to improve quality of life and life expectancy of kidney transplant patients.

An EU funded project—TTV GUIDE TX—has kicked-off to establish a tool to quantify the activity of the immune system in kidney transplant patients and, thereby reducing infections and organ rejections.

If the kidneys stop working, a kidney transplant can restore their function. However, the immune system would recognize the new kidney as foreign and attack it.

Therefore, kidney-transplant recipients need drugs to reduce the function of their immune system. These drugs are called immunosuppressive drugs. If the patients take too many drugs, their immune system is weak, and they get infections. On the other hand, if they take too few drugs, they have an increased risk of organ rejection.

Therefore, transplant physicians require a tool to quantify the activity of the immune system and optimize the drug dose. The recently discovered TT virus might do this job: TT is naturally occurring in the blood of almost every healthy person and every kidney transplant recipient, and it causes no disease.

If the immune system is functioning properly, the TT virus load is low; this indicates a risk for organ rejection. If the immune system is suppressed too efficiently by medication, the TT virus load is high; this indicates a risk for infection.

The quantification of the TT virus load in the blood of kidney transplant recipients might help to optimize the dosage of immunosuppressive drugs and thus to reduce infections and rejection. Within the TTV GUIDE TX project, TT virus guided dosing of immunosuppressive drugs will be tested in a clinical trial including 260 kidney transplant recipients from all over Europe. Once established in routine clinical care, TT virus monitoring might reduce thousands of infections and kidney transplant rejection each year. In the future, the TT virus might not only help kidney transplant recipients but also patients with liver, heart and lung transplantation and therefore guide therapy in autoimmune, infectious and oncologic diseases.

Coordinated by the Medical University of Vienna (Austria), the TTV GUIDE TX brings together 19 partners, including kidney transplant physicians, clinical virologists, project and clinical trial managers, ethicists, and health care industry professionals, from 7 EU countries to run a clinical trial with almost 300 patients.

The TTV GUIDE TX project will work closely together with The European Kidney Patients' Federation (EKPF), the European umbrella organization for 23 national kidney patients' associations.

The TTV GUIDE TX project will participate in the Pilot on Open Research Data in Horizon 2020, which aims to improve and maximize access to and reuse of research data generated by EU funded actions.

The project officially started on 1st May 2021, for a duration of 60 months. It has received support from the European Union Framework Programme for Research and Innovation Horizon 2020 with a total budget of €6 Million.

Ethical Framework

Human subjects research

What is research?

There is no agreed or universally shared definition of what *research* is. The *British Research Assessment Exercise* (RAE) defines it as follows:

> "'Research' . . . includes work of direct relevance to the needs of commerce, industry, and to the public and voluntary sectors; scholarship; the invention and generation of ideas, images, performances, artefacts including design, where these lead to new or substantially improved insights; and the use of existing knowledge in experimental development to produce new or substantially improved materials, devices, products and processes, including design and construction. It excludes routine testing and routine analysis of materials, components and processes such as for the maintenance of national standards, as distinct from the development of new analytical techniques. It also excludes the development of teaching materials that do not embody original research".
>
> *HEFCE, SHEFC, HEFCW, & DEL, 2008.*

What is human research?

Human research is carried out with or on people, their data or tissues. The participation of human subjects in research is understood broadly and involves:

- taking part in surveys, interviews or focus groups;
- undergoing psychological, physiological or medical testing or treatment;
- being observed by researchers; researchers having access to their personal documents or other materials;
- the collection and use of their body organs, tissues or fluids (e.g., skin, blood, urine, saliva, hair, bones, tumour, and other biopsy specimens) or their exhaled breath; and

access to their information (in individually identifiable, reidentifiable or nonidentifiable form) as part of an existing published or unpublished source or database.

Why does clinical research require an ethical review?

Human subjects involved in research serve to gain that knowledge. However, there is a risk that these clinical trial participants are exploited or abused. Ethical requirements are a way of limiting these risks of exploitation. One of the main reasons for the need for an ethical review of research is to ensure that research is responsibly conducted, and in line with the *Declaration of Helsinki* (WMA, 2013).

It is important to respect ethical principles to protect the dignity, rights and welfare of research participants. As such, all research involving human beings should be reviewed to ensure compliance with ethical standards. Consideration of some basic ethical principles such as justice, equity, beneficence, and autonomy are crucial for any research involving human subjects.

Ethical Review Supports Maintaining High Standards of Research Conduct and Hence Improves the Quality of Research results. Responsible Research and Innovation

The right to science is recognized in the 1948 *Universal Declaration of Human Rights*:

> "27 (1) Everyone has the right to freely participate in the cultural life of the community, to enjoy the arts and to share in scientific advancement and its benefits".
>
> *UN, 1948.*

The vision of science as the basis for a prosperous society emerged some years before, in 1945 with Roosevelt, who had in mind that after the ravages of war, science would take a central role in building a new society, not only in North America but also throughout the world ("FDR and the Four Freedoms Speech", 2016).

These ideas germinated in the development of the institution we know today as UNESCO.

Preceding the foundation of UNESCO, the public perception of the sciences and scientists was marked by mistrust and suspicion since science in general was involved in the worst episodes of World War II: the inhuman experiments carried out by Nazi doctors and the development and use of two atomic bombs in Hiroshima and Nagasaki (Japan).

UNESCO helped to restore the image of science and put science at the service of moral values and objectives. As stated in its statutes:

> "UNESCO is the United Nations Educational, Scientific and Cultural Organization. It seeks to build peace through international cooperation in Education, the Sciences and Culture".

Responsible Research & Innovation (RRI) (Regulation 1291/2013)[1] is a process that

[1] There are different websites and tools developed to make the RRI framework more accessible to researchers and the public: https://www.fosteropenscience.eu/content/practical-guide-responsible-research-and-innovation, https://tetrris.eu/what-is-responsible-research-and-innovation-rri/, https://www.ukri.org/about-us/policies-standards-and-data/good-research-resource-hub/responsible-innovation/, and https://rri-tools.eu/

takes the wider impacts of research and innovation into account by anticipating and assessing its potential implications and societal expectations in order to make research and innovation inclusive and sustainable. RRI has been used in the Horizon 2020 programme to group crosscutting concepts of societal aspects of science and innovation within the objective of the Science with and for Society (SwafS) agenda. It also plays a major role in the Horizon Europe programme. RRI aims to engage a broad range of stakeholders to discuss how science and technology could be used in the best possible way not only to contribute to solving today's problems, but also to think and considering future generations.

Research and innovation have improved our lives in many ways. However, science and technology sometimes create new risks and ethical dilemmas. They can generate controversy and not solve problems or create new issues of concern. RRI responds to different challenges by engaging all stakeholders (researchers, governments, citizens, etc.) through inclusive and participatory methodologies. To be effective, participation takes place at all stages of the process and at all levels (from program planning to design, implementation, and evaluation). Research and innovation will address societal challenges and align with the values, needs, and expectations of the public.

Five key areas of RRI

1. Gender equality: addresses gaps between women, men, and gender diverse individuals by ensuring that gender dimensions are taken into consideration in research and innovation, in decision-making, the allocation of funding, and in the composition of teams and organisations, among other aspects.
2. Open access: aims to make science transparent and accessible. The results of publicly funded research (publications and data) should be made freely accessible for public use online.
3. Citizen engagement: emphasizes that the public should jointly participate in the research and innovation process, and not only the traditional pillars of researchers, industry, and policy makers. Citizen engagement includes civil society organisations.
4. Science education: confronts the challenge of better preparing future researchers and other social actors, providing them with the tools and knowledge necessary to participate fully in the process of research and innovation, as well as equipping citizens to take part in forming science policies.
5. Ethics: to respect fundamental rights and the highest ethical standards in order to guarantee greater social relevance and greater acceptance of the results of research and innovation.

Informed consent process in clinical research

Informed consent is essential in research. In the context of the TTVGUIDE IT trial, it can be defined as the process by which a participant is informed about all aspects of the trial, which are important for the participant in decision-making. After studying all aspects of the trial, the participant voluntarily can confirm or not his or her willingness to participate. In this process, healthcare professionals and researchers should listen to and respect the participants' opinion in the decision-making process. The main goal of informed consent in both clinics and research is to foster the person's autonomy in the process, and to guarantee her protection against possible abuses that can arise in biomedical interventions or research (Rodríguez-Arias et al., 2008).

The requirements for informed consent in clinical research are more demanding as compared to those for consenting to clinical

treatment. Individual benefit does not automatically follow from research interventions, and the degree of potential risks is increased. It may require a higher capacity level for consent. The informed consent must be obtained in a written form, after exhaustive information about the details that are relevant for the participant. Participants in clinical studies have the right to receive detailed information about the research in order to make a free, informed and voluntary decision.

Due to the process of research itself, clinical research interests are not necessarily aligned with the individual interests. Thus, in all clinical research the investigators may face conflicting interests between the principle of individual safety and benefit, on the one hand, and the imperative of the collective interest and increased knowledge, on the other hand (Rodríguez-Arias et al., 2008). The purpose of informed consent in research is to prevent science and society from unduly taking advantage of individuals whose consent is defective. Numerous factors can subvert the quality of informed consent in clinical research, as shown below:

Table 1

Types of undermined consent	Definition
Consent undermined by coercion (Millum & Garnett, 2019)	Occurs when a proposal constitutes a threat to someone's rights or fails to discharge some duty owed to others (e.g., when consent to a contract is induced by fraud, misrepresentation, coercion, or undue influence).
Coercion as subjection (Millum & Garnett, 2019)	It constitutes a type of harm. In this type of undermined consent, a person is coerced into doing something if that person is subjected to another person's will (e.g., payment to a research participant).
Therapeutic misconception (Appelbaum et al., 1982)	Occurs when participants/patients, as well as clinicians or researchers attribute therapeutic intent to research.

The type of coercion as subjection (Millum & Garnett, 2019) is reflected in clinical contexts where the patient is in a desperate situation to get treatment for their condition and no one has forced him/her against their will to participate in a clinical trial, so it cannot be said that their consent has been undermined, but it is true that their consent has been conditioned. The asymmetry of power in the doctor-patient relationship may be another instance of coercion as subjection where true consent is undermined (Faden & Beauchamp, 1986).

To avoid such factors that may undermine consent, a number of prerogatives or rights of the patient and/or participant in a medical intervention have been stipulated, namely the right to information and the right to withdraw.

Right to be informed

Informed consent from potential research enrolment is a standard and obligatory way to respect the autonomy of participants. Consent is a process and it includes the conversation between the researcher and the potential participant. An individual has the right to be informed even after giving consent, as well. Those responsible for the investigation should be able to provide the participant with concise, intelligible, easily accessible, and clearly written information about the research in which the person is going to be involved. However, there is some uncertainty about whether the participant has reliably understood the

information. The right to consent could easily be undermined by incomplete information. However also when full information is provided, but the researcher does not assess to what extent the participant really understood the provided information, consent could be subverted.

In clinical research, the following categories of information therefore must be provided (Manti & Licari, 2018):

ETHICALLY VALID CONSENT

For an ethically valid consent, information provided to a research subject should include, but is not limited to:

- Information about the health condition for which the research is proposed
- Details of the nature and purpose of the research
- The expected duration of the subject's participation
- A detailed description of study treatment or intervention and of any experimental procedures (including, in the case of randomised clinical trials [RCTS], also blinding and randomisation)
- A statement that participation in research is voluntary
- Probable risks and benefits associated with research participation
- Details of the nature of the illness and possible outcome if the condition is left untreated
- Availability, risks and benefits of alternative treatments
- Information about procedures adopted for ensuring data protection/confidentiality/privacy, including duration of storage of personal data
- Details about the handling of any incidental findings of the research
- Description of any planned genetic tests
- Details of insurance coverage in case of injury
- Reference contacts for any further answers to pertinent questions about the research and the subject's rights and in case of any research-related injury to the subject
- Any other information that seems necessary for an informed decision to be taken by the subject
- A statement offering the subject the opportunity to withdraw at any time from the research without consequences
- Specific information should be provided in case of research projects involving children, incapacitated adults not able to give informed consent, illiterate populations, and so forth.

The amount of information to be provided would vary according to the risks and the particularities of the research to be undertaken.

For instance, in the case of the TTVGUIDE IT trial there is no processing of genetic information although biomaterial samples will be collected and stored in a biobank beyond the end of the study and made available for medical research.

As part of the TTVGUIDE IT trial, patients are entitled to:

- understand that participation is voluntary;
- ask questions and receive understandable answers before making a decision;
- know the degree of risk and burden involved in participation;

- know who will benefit from participation;
- know the procedures that will be implemented in the case of incidental findings;
- receive assurances that appropriate insurance coverage is in place;
- know how their biological samples and data will be collected and protected during the trial;
- know of any potential commercial exploitation of the research.

***** In addition to the information patients will receive about the clinical trial, they will also be informed, independently and outside this trial, whether they want to give their urine and blood samples to be stored in a biobank, and that they will be informed about how these samples may be used in the future, including the fact that they will no longer be asked for consent to use them to obtain genetic information in the future.

Right to withdraw

The right to withdraw is one of the fundamental concepts in the ethics of research. Each participant must be informed of his or her right to withdraw at any time without reprisal (WMA, 2013).

One of the earliest documents on human research, the Nuremberg Code, includes the right to withdraw, conditional or restricted in comparison to its more modern version, where the right to withdraw is "unconditional and requires no explanation or justification" (Holm, 2011).

While the Nuremberg Code includes the possibility of terminating an intolerable intervention, the Declaration of Helsinki and the World Medical Association's statement of principles for medical research, expand the right to add that there should be no reprisal for such termination. For example, in the 64th *Declaration of Helsinki*, which was adopted by the WMA General Assembly, in Fortaleza, Brazil, October 2013; Article 26, and we quote in full, states (WMA, 2013):

> "In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information".

In the TTVGUIDE IT trial, all subjects have the right to withdraw at any time during the study without prejudice.

This must be communicated clearly and often to the participants. In addition, there will be continuous safety and efficacy follow-up for each subject. Consequently, if any of the following

circumstances appear, they constitute signs for withdrawal of the patient, and participating researchers will be alert of them:

- withdrawal of consent by the patient/legal representative;
- any clinical condition that, in the investigator's opinion, could constitute a risk to the patient and that would prevent the appropriate conduct of the trial; and
- loss of capacity to consent.

Respect for participants who need special protection or cannot consent

Certain persons enrolled in clinical projects as participants who are particularly vulnerable and unable to protect their interests cannot provide unambiguous and voluntary informed consent.

These persons may have difficulty understanding the risks and benefits of research, and their ability to consent may be compromised. For this reason, in the event that it is strictly necessary to obtain the consent of these persons, this must be done with extreme care, guarantees and always respecting their rights.

Patients may have different intellectual capacities, and this implies a qualitative difference in the understanding of the information and risks associated with research. No one can substitute for the consent of a competent adult, but the law provides for exceptions in the case of minors, persons with disabilities and mental illness.

In the case of the TTVGUIDE IT trial, there are some groups of persons who may need special protection, and consequently, will not be included in the study: underage persons; pregnant and breastfeeding women; adults who are not able to recognise the nature, significance and scope of the clinical trial and to orient their will accordingly; persons who are unable to give informed consent; and persons who are accommodated in an institution by court or official order. In addition, immunological high-risk patients will also be excluded.

Power imbalance between participants and researchers, especially when researchers are the clinicians

In biomedical research, an important figure is the clinician-researcher (also referred to as the clinical scientist and the scientist-practitioner): the professional who both conducts research and provides direct services to the patients (Yanos & Ziedonis, 2006). Although clinician-researchers are undoubtedly valuable and necessary to conduct good quality biomedical research, there are some ethical challenges, posed by the involvement of clinicians in research that includes human participants. In clinical studies, there can be conflict between the interests of the individual participant and the scientific aims of the study. Consequently, "the clinician-researcher may experience a conflict between the clinical mandate to act in the patient's best interest (beneficence) and the scientific mandate to pursue truth with all appropriate rigor (scientific autonomy)" (Yanos & Ziedonis, 2006). In the clinical setting, we can distinguish mainly four relationship models (Emanuel & Emanuel, 1992):

Table 2

Relationship models	Characteristics
Paternalistic model	The autonomy of the patient is not taken into account and the health professional acts as a tutor.
Informative model	A clear distinction between facts and values is proclaimed: the professional must provide objective information about the facts and the patient, after receiving the information, decides based on his own values.
Interpretive model	The professional, in addition to informing, acts as a counsellor, helping the patient to interpret the information and decide which of the possible alternatives best fits her value system.
Deliberative model	The professional, after providing all the pertinent information, engages the patient in a deliberative dialogue to establish which course of action would be the most appropriate in each case.

The deliberative model implies a collaborative work, in which dialogue plays a central role. The same respect for autonomy requires that the healthcare providers make recommendations and guide the patient based on their knowledge, their experience, but also and above all based on an adequate understanding of the values and objectives of each person (Goberna-Tricas, 2018). Dialogue and deliberation become essential factors in decision-making. People's values are not assumed as something fixed and unquestionable − as the informative model presupposes − but as changing, dynamic values, subject to reconsideration and for this reason dialogue and deliberation become essential factors in decision making. The deliberative model has been emphasized as the most suitable in the clinical context. In research, however, the appropriate relationship model is an informative model, especially when the clinician-researcher is the healthcare provider of the patient who potentially can be involved in the research. A clinician who is also a researcher must be extremely cautious to try to be neutral in the information. The role of the clinician-researcher as a recruiter is strictly informative, and no persuasion or influence in the decision-making process can be acceptable. To ensure the voluntary and free consent of participants is one of the most important duties of recruiters. Thus, helping patients understand the differences between clinical practice and clinical research must be a duty. Patients need to understand that although individuals may receive treatment in both clinical practice and clinical research, the orientation of these activities is markedly different. While clinical practice is oriented toward providing patients with individualized care by physicians who are dedicated primarily to their patients' best interests, clinical research is oriented toward developing knowledge to help future patients. Patient–participants may benefit from research participation, but this is not the primary purpose of research (Chen et al., 2003). The researchers need to ensure that the participants comprehend this difference, as well as all the relevant information about the clinical trial in itself.

The "Ethical, Legal and Social Implications" (ELSI) study, as part of the TTV GUIDE TX project, could partially fulfil the deliberative function, by addressing the experiences and different views of

participants and healthcare professionals involved in the clinical trial. The study may help future research design and performance to include the perspective of participants about the informed consent process or therapeutic misconception problems. The ELSI study carried out by Work Package 2 (WP2) Ethics and Governance (University of Granada) aims to get first-hand feedback from professionals and patients involved in the TTV GUIDE TX project.

How to assess the comprehension of the information? Measures/tools that need to be developed to support understanding in the information process

A fundamental aspect of informed consent is a clear understanding of the risks and benefits associated with a medical intervention.

In the case of the TTVGUIDE IT trial it is key to understand that a clinical trial will be launched to compare the safety, tolerability and preliminary efficacy between standard and torque teno virus-guided immunosuppression in stable and immunological low-risk adult kidney transplant recipients.

To ensure understanding, a way of assessing comprehension must be found because the mere disclosure of information does not ensure that. Even when the information is provided in a simple and common language, many participants may not fully understand the statistical information about the risks. They also might not fully understand the fact that in the trials, participants might not receive the active treatment under investigation, but the standard treatment, or the fact that clinical trials aim to further scientific knowledge and not their own medical good.

This can lead to “therapeutic misconception”, where participants tend to overestimate the benefits and underestimate the risks of participating in a clinical trial, as we will see below. Providing adequate information in a clear manner to facilitate understanding and make the effort or provide the opportunity for the participant to ask questions to clarify doubts are indispensable prerequisites for assessing the comprehension of information.

The most basic tool for improving understanding of medical information to provide informed consent is plain language. Common terms and words should be used to explain information to patients.

Patients are to be encouraged to take notes to be used during briefings to enable them to assimilate the information conveyed. The use of printing brochures, in addition to the ethical and legal requirement of information sheets, are very useful tools. It is also necessary to use methodologies to assess the comprehension of the information conveyed. Printed brochures presenting supplementary and additional information on the purpose of the clinical study may allow for a better understanding of the objectives of the intervention.

Another very useful tool to ensure comprehension of information and thus provide unambiguous informed consent is the use of multimedia or audiovisual material. Audiovisual tools allow for effective and direct understanding of information which, when transmitted verbally, could be hindered by socio-cultural differences. Several studies have shown that audiovisual tools improve the understanding of the informed consent process (Jimison et al., 1998; Synnot et al., 2014). The main intention of using multimedia and interactive tools is to convey complex information in an easy and understandable way to potential patients or clinical study participants who have low health literacy. All these tools are not meant to replace the conversation, but to be used in addition for better understanding.

The TTV GUIDE TX project provides several audio-visual materials in the project's website (https://www.ttv-guide.eu/) aimed to help participants—participants will also receive an information folder about the study—and any individual interested on the project to better understand different aspects of the project. In addition, to enhance visibility and recognition of the project, the project consortium developed a logo and a corporate identity for all communication materials, including Microsoft PowerPoint and Word templates, standard presentations, project leaflets, and other tools such as a Frequent Asked Questions section placed on the website.

Therapeutic misconception

Therapeutic misconception is intimately related to the difficulties of comprehension that participants have when enrolled in a biomedical study. In 1982, Paul Appelbaum, Loren Roth, and Charles Lidz coined the term "therapeutic misconception" (Appelbaum et al., 1982) to describe the tendency of individuals enrolled in clinical trials to confuse the scientific orientation of their research participation with the therapeutic orientation of medical care. 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, 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 (Yanos & Ziedonis, 2006).

In practical terms, what clinical trial managers need to ask themselves is how to avoid therapeutic misconception and thus obtain quality informed consent. Therapeutic misconception can occur in multiple clinical trials but perhaps one of the traditional readings of Appelbaum et al.'s idea has been its implications for randomized controlled trials.

From this standard interpretation and applied to randomized controlled trials, it has been

presumed that participation in such clinical trials is clearly disadvantageous when a participant is placed in the control arm. Under this disadvantage thesis, clinical trial participation, mainly placebo-controlled trials, necessarily disadvantages subjects by exposing them to predictably inferior outcomes and therefore leads to therapeutic misconception.

Understanding whether this disadvantage really exists allows us to understand the ethical significance of therapeutic misconception and to consider adequate policy actions. There are authors who supposedly present empirical evidence that refutes the disadvantage thesis that leads to therapeutic misconception, but according to Appelbaum and colleagues in randomized controlled trials, certain participants are kept at a great disadvantage due to the nature of the research process itself.

DISTORTED ASSESSMENTS OF THE POTENTIAL BENEFITS AND RISKS OF PARTICIPATING IN RESEARCH

(Chen et al., 2003):

- Patients may falsely believe that novel interventions, although experimental, are always better than standard available treatments.
- Patients may confuse invitations to participate in research with individualized recommendations for treatment.
- Even patients who are fully informed and who understand the purpose and procedures associated with research can believe that the treatment they receive as part of their participation has been individually determined to be the best option for them.

In addition, clinicians should assess their own purposes regarding clinical research and reflect whether they may be contributing unintentionally to therapeutic misconceptions (Grieselhuber et al., 2017). When a patient is participating in a clinical trial, the physician should assess the patient's understanding of the goal of the study and take responsibility for the patient's protection.

FACTORS THAT CONTRIBUTE TO THERAPEUTIC MISCONCEPTIONS

(Grieselhuber et al., 2017)

Distorted assessments of the potential benefits and risks of participating in research are (Chen et al., 2003):

- The public often has a poor understanding of the research, being difficult for people to define the basics terminology such as "randomized", or "double-blind"
- The patient's trust in the clinician may lead to think that if the doctor recommends a clinical trial, this will treat the disease
- The media often sensationalize the results of some studies, reinforcing patients' assumption that experimental treatments are very likely to be successful

- An individual physician may be both a clinician and a researcher, which can confuse the patient.
- Some institutions may present participation in clinical trials as a way to gain access to new treatments before they are widely available to the general public.

Physicians and researchers may knowingly or unknowingly overstate possible benefits while minimize risks, demonstrating provider bias to support their own beliefs or perceptions about certain treatment methods. In these cases, “clinicians themselves may be operating under a therapeutic misconception, truly believing that a trial represents the best possible treatment option for a particular patient” (Grieselhuber et al., 2017).

Several ways to address these issues related to therapeutic misconception have been proposed, as identified by Yanos and Ziedonis (2006).

The first approach suggests that patient-oriented clinician-researchers should avoid having direct research contact, such as recruitment, if they have a therapeutic relationship with the individuals. However, there are more subtle ways in which a clinician’s involvement can sway an individual to participate or remain in a study, for instance, if a patient sees the name of a trusted clinician on a list of investigators. Thus, it is necessary to complement this recommendation with other approaches to adequately address conflicts of interest.

The second approach identified recommends that patient-oriented clinician-researchers never conduct research with vulnerable individuals when there is any risk of exploitation or harm. This position may be too restrictive, since it takes away individual autonomy from participants. Not only on the individual level, but to a whole vulnerable group, it might also preclude research for this group which is a sort of harm (e.g., in case of minors).

The third approach recommends that clinician-researchers fully disclose their conflicts to potential research participants. However, if the participants receive the message that there is no real conflict, then it will not influence their decision process.

The fourth approach states that clinician-researchers must seek an integration of their dual roles and develop a “coherent moral identity” that promotes good ethical judgment. This approach emphasizes “that clinician-researchers be aware of themselves and the possibilities for exploitation in their studies and take extra care to develop a relationship with participants that minimizes the possibility for therapeutic misconception” (Yanos & Ziedonis, 2006). Clinician-researchers should be aware that they have an ethical responsibility to both the individual patient and to society.

Yanos and Ziedonis (2006) concluded that the establishment of integrated identity is ultimately the most comprehensive means of balancing and prioritizing ethical issues and resolving conflicts of interest, since awareness uses judgment to take appropriate steps.

A related situation has been called therapeutic optimism (Grieselhuber et al., 2017): patients may know that participation in research may not help them, but they strongly hope that it will. The patient may estimate the chances of treatment success in a way substantially higher than the research team. Consequently, in this case, the decision-making process requires understanding the patient’s expectations regarding the clinical trial and deciding whether they constitute a therapeutic misconception or therapeutic optimism.

Recommendations regarding therapeutic misconception in TTV GUIDE TX PROJECT

This must be communicated clearly and often to the participants. In addition, there will be continuous safety and efficacy follow-up for each subject. Consequently, if any of the following circumstances appear, they constitute signs for withdrawal of the patient, and participating researchers will be alert of them:

- As part of the TTV GUIDE TX project, it is unavoidable that the clinicians are the researchers too.
- Physicians treating patients who are participating in a clinical trial should assess the patient's understanding of the purpose of the study and take responsibility for the patient's safety.
- In addition, clinician-researchers must be cautious to avoid therapeutic misconception, especially because in this trial, the intervention is not a completely new drug (tacrolimus), but a new manner how immunosuppression is guided.
- Due to that, we recommend to follow particularly that the clinician-researchers fully disclose their conflicts, and that clinician-researchers be aware of their own double role, and take extra care to develop a relationship with participants that minimizes the possibility for therapeutic misconception. In addition, regarding persons who need special protection, they will not be included, as explained on page 18.
- Discuss the patient's expectations of the clinical trial and proceed only when the patient has an accurate understanding of the situation.
- The ELSI study, as part of the TTV GUIDE TX project, has been designed as a strategy to assess the therapeutic misconception risk for both participants and healthcare professionals involved in the clinical trial. It is expected that the results of this study can shed more light about how to avoid therapeutic misconception in clinical trials by including the participants' perspective.
- The WP2 Ethics and Governance has designed some audio-visual materials to appear in the website https://www.ttv-guide.eu/ to inform participants and professionals about the ethical aspects of informed consent and the risks of therapeutic misconception

Additional findings

Additional findings are usually defined as observations, results, or other findings that may occur during analysis/research but are unrelated to the goals of the analysis/research. Additional findings go beyond the purpose of the research and often beyond the researcher's expertise. They can be divided into three categories:

Table 3

Type of result discovered	Description	Example
Primary finding	Practitioner aims to discover A, and the result is relevant to A.	In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered.

Type of result discovered	Description	Example
Incidental finding: Anticipatable	Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place.	Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related.
Incidental finding: unanticipatable	Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place.	When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not known at the time a previous sample was submitted.
Secondary finding	Practitioner aims to discover A, and also actively seeks D per expert recommendation.	ACMG recommends that laboratories conducting large-scale genetic sequencing for any purpose should actively look for variants underlying 73 genes.

Source: Presidential Commission for the study of Bioethical Issues (2013, December). *Anticipate and Communicate: Ethical Management of Incidental and Secondary Findings in the Clinical Research, and Direct-to-Consumer Contexts*. PCSBI, p. 27. **Note:** DTC = direct-to-consumer, ACMG = American College of Medical Genetics and Genomics.

From an ethical point of view, incidental findings raise multiple issues. For example, it could relate to the duty of care and the duty to warn participants in an investigation. Another question refers to the management of such findings by researchers.

From the perspective of researchers, these types of questions are not only practical but also ethical. How should an incidental finding be handled in a clinical context? How should the welfare of the participant be protected? Who is responsible for communicating an incidental finding?

From the participant's perspective, there are also important ethical issues that can arise. Consenting to participate in a study or clinical trial where incidental findings are potentially possible can lead to anxiety or panic in the face of serious negative news. In certain jurisdictions it is possible that incidental finding reporting may also have implications for insurance policies and so on.

Another significant issue is that in some clinical trials the person responsible for communicating incidental findings is not an expert and does not have the necessary skills to manage this type of information. This is important in cases where participants are particularly vulnerable.

Perhaps the most serious incidental finding is identification of a previously undiagnosed medical condition during the course of a study or clinical trial whose purpose was research. If we add to this the fact that this finding may be genetic, this would mean that it would not only concern a single individual but very possibly also related family members.

Whether or not to communicate incidental findings is a crucial issue. Much concern about incidental findings has been expressed about the right of individuals not to receive certain information, particularly about incurable conditions. If this is the case, some would prefer to remain in ignorance. Individuals have a right not to know certain information about themselves, and the right to refuse receiving information on certain incidental findings (Schaefer & Savulescu, 2018). Thus, it is important that the patients are informed of the

possibility of discovering incidental findings (if any) and they have a way to express their preferences regarding their wishes to know or not about this information.

Patients' right to exercise their choice not to know is another important aspect to consider. Studies exploring this issue show that, in hypothetical situations, a high proportion of people want to receive all types of genomic sequencing results, in some cases regardless of whether or not they are actionable (Isidor et al., 2019). National and supranational bodies, for example the European Union in the case of research carried out in member states as in the case of TTV GUIDE TX, ensure (EC, 2019) that there is an incidental finding policy when it comes to research involving human subjects in order to cover the minimal possibility of their appearance. Researchers must communicate the fundamental aspects of their research, which include the possibility of discovering incidental findings and the willingness to search or not secondary findings and the plan for their management. By doing so, participants can make fully informed decisions whether to enrol. From the beginning, researchers can ascertain what participants prefer to know, and not know, about incidental or secondary findings, which helps researchers to respect participants' autonomy.

INCIDENTAL FINDINGS

The main steps of the risk assessment of incidental findings are:

1. Identify potential incidental finding
2. Recognize and list incidental findings
3. Manage incidental findings by categorizing and evaluating them. Elaborating an incidental findings communication protocol for both pre-test and post-test information.
4. Apply the protocol: Communicate them or not to research participants, depending on each participant choice
5. Design a follow-up policy

SECONDARY FINDINGS

The main steps of the risk assessment of secondary findings are:

1. Identify potential secondary finding
2. Decide whether or not to search for secondary findings. If yes:

- Define the gene list.
- Elaborating a secondary findings communication protocol
- Apply the protocol: Communicate them or not to research participants, depending on each participant choice
- Design a follow-up policy

Source: made by the authors.

An important aspect to take into account is that the intention of informing participants about findings is to avoid unduly alarm or to negatively affect the study's recruitment of participants. Researchers should only include anticipatory information about incidental or secondary findings in the information consent letter when there is a real possibility and

probability that an incidental or secondary finding will be uncovered; and there are clinical and therapeutic implications. If the goals of the research include secondary findings to support secondary research objectives, this should be disclosed to the participants during the consent process. This disclosure should include the rationale for seeking the secondary research findings.

The TTVGUIDE IT trial will enrol kidney transplant patients, and it will start three months after the transplantation. To be more specific, it includes a screnning period in the 1st three month post TX and the interventional trial will start in month 4 post tx and will continue until month 13 post TX covering the 1st year post TX. Due to that, the participants will undergo routine tests in the course of post transplantation care that will be done according to extant policies in each centre. The TTV GUIDE IT clinical trial does not affect or interfere with already established screening and diagnostic procedures with transplant candidates. The only specific test that will be conducted is TT virus monitoring, which is independent of the routine follow-up of kidney transplant patients. Therefore, no incidental or secondary findings associated with the TT virus test are expected, and consequently, no specific incidental findings' policy is judged necessary. However, samples and biomaterials will be stored in a biobank beyond the end of the TTV GUIDE TX project. These biomaterials will be stored for an indefinite period of time and made available for future medical research. Patients are not going to receive more information about the type of studies or results that will take place with their biomaterial according to the informed consent form.

Confidentiality

Confidentiality is a right based on privacy, but confidentiality is different from privacy. Privacy is informational self-determination directly related to data protection rights. For its part, confidentiality is much more than privacy, and it comprises much more than data protection rights. Confidentiality comes second to privacy and for confidentiality to be triggered, privacy must have been breached.

Historically, understanding the real meaning of confidentiality involves taking into account a main dimension of confidentiality, which is the right to confidence. According to Lord Goff of Chieveley ("Attorney General v. The Observer Limited", 1988), the duty "(…) arises when confidential information comes to the knowledge of a person (the confidant), with the effect that (…) he should be precluded from disclosing the information to others".

Today, the right to privacy and the right to confidentiality are regulated under the General Data Protection Regulation (GDPR). Every sponsor/investigator is required to record, process, store, and handle data in such a way that preserves the confidentiality of records and data and to apply appropriate technical and organizational measures to protect information and personal data (Article 56 of Clinical Trials Regulation).

In this sense, principal investigators and their research teams are obliged to maintain patient/participant confidentiality within the context of clinical trials. The confidentiality of medical records and the personal data of subjects should be protected in accordance with the applicable law on the protection of personal data (in the European context the GDPR).

In clinical trials databases protected under applicable law, there is a tension between transparency and confidentiality. Most of the information collected in European databases must be transparent and freely accessible, but exceptions must of course be made for reasons of confidentiality.

Within TTV GUIDE TX project, data will be treated according to EU regulation 2016/679. Detailed information will be provided to the local authorities and local IRBs on privacy/confidentiality and the procedures that will be implemented for data collection, storage, protection, retention, and destruction. Some transfer of data between EU countries will be required. We will always obtain the necessary notifications/authorisations for collecting and processing the data (including specific authorisations, if applicable).

Anonymization

Until now, most clinical trial information has remained confidential. This has changed with the entry into force of new legislation, such as the European Medicine Agency (EMA)'s Policy 00701 and the European Union (EU)'s new clinical trial regulation (CTR) 536/2014. This new regulatory framework has allowed expanded public access to clinical trial data.

These new disclosure rules apply to clinical trial results and to anonymized patient data. In this new regulatory framework, transparency is a key value. Under the transparency policy, all clinical reports will be subject to publication and may even be subject to third party access.[2] As for any public authority, all clinical reports submitted as part of a regulatory application should be as open as possible.

Nonetheless, transparency needs to be balanced with the protection of patient's privacy through the anonymization of their data. Anonymization is a process, which consists in rendering data into a form where individuals cannot be identified and where identification will not occur. Inadvertent disclosure of patient identifiable information must be prevented through a number of different strategies of de-identification.

Some strategies for de-identification are deletion, redaction, generalization, perturbation, or dissociation of identifying information. In accordance with the GDPR, although transparency in clinical trials should be pursued as a fundamental value, all data controllers should ensure a reasonable degree of anonymization.

Anonymization helps to protect the privacy of patient or trial participant data and limits the wide dissemination of personal information by

[2] European Medicines Agency (EMA).

regulatory agencies or sponsors when publishing the results of a clinical trial.

Within the TTVGUIDE IT trial, confidentiality will be secured for personal and medical information relating to individuals taking part in the study according to individual local data protection legislation and current guidelines of Good Clinical Practice (GCP).

Pseudonymization

There is often some confusion between anonymization and the clearly different concept of pseudo-anonymization. ISO/TS 25237:2017, which contains principles and requirements for privacy protection using pseudonymization services for the protection of personal health information, defines *anonymization* as:

> "a process by which personal data is irreversibly altered in such a way that a data subject can no longer be identified directly or indirectly, either by the data controller alone or in collaboration with any other party".
>
> *International Organization for Standardization, 2017.*

The NIST (National Institute of Standards and Technology, US Department of Commerce) defines *anonymization* as:

> "a process that removes the association between the identifying data set and the data subject".
>
> *NIST, n.d.*

An anonymized database prevents the identification of an individual by the controller or a third party.

Removing a user's identifier is a prerequisite for anonymization, but it is not sufficient to guarantee anonymity. In order to ensure anonymity, it is necessary to apply a number of techniques.

Two main approaches to ensure anonymity are "randomization" and "generalization techniques". Randomization alters data via noise addition, whilst the generalization techniques modify specific attributes, such as replacing the exact age by an age range in order to prevent singling out.

To sum up, pseudonymization is related to the existence of an association between personal identifiers and

pseudonyms, whilst in anonymization such association should not be available by any means. In other words, pseudonymised data are still personal data, while anonymized data is not. Some benefits of pseudonymization for data protection is to hide the identity of data subjects while allowing for reidentification if required, for example, to communicate an incidental finding with potential benefit.[3]

[3] See: European Union Agency for Cybersecurity, 2019. More information about this issues in Kohlmayer et al., 2019.

For the TTV GUIDE TX project, the University of Granada (UGR) is tasked with monitoring all aspects of data protection. UGR will check whether data are treated according to EU regulation 2016/679 (e.g., pseudonymization, security measures to prevent unauthorised access, and sampling according to data minimisation principles). The sponsor ensures that researchers will allow monitoring and audits related to the data by providing direct access to the source data/documents.

Data protection

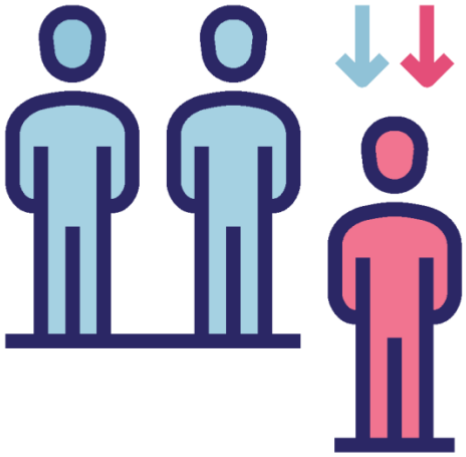
In clinical trials, there is an interplay between the Clinical Trials Regulation (EU) 536/20141 and the General Data Protection Regulation (EU) 2016/679 (GDPR). The clinical trial protocol, authorized under the Clinical Trials Regulation, defines the purposes and conditions for which the data of clinical trial subjects will be processed. Participants will be informed at all times of the processing of their personal data. GDPR applies to any clinical trial that collects personal data from citizens of the European Economic Area (EEA).

- The lead Clinical Trial Unit (CTU), who is responsible for providing the data management plan, will perform data management for the TTVGUIDE IT trial. Data will be collected at each site and entered into the electronic case report form (eCRF). All relevant recipient and donor baseline characteristics and data regarding primary and secondary endpoints will be entered. Data will be sampled according to data minimization principles. Personal data will be processed according to principles that aim to limit the potential for detrimental impact on the subjects concerned and to ensure data quality and confidentiality.
- Within the clinical study, confidentiality will be secured for personal and medical information relating to individuals taking part in the study according to individual local data protection legislation and current guidelines of GCP. In local databases, personal identities will be protected by using coded identities to indicate the subjects. The file matching subjects personal data with study IDs will be kept only by the partner who collected the information (clinical partners). All personal data will be pseudonymised upon collection in the clinics. The key remains with the local clinics, and only these clinics will be able to link the data to the patient. Data for publication purposes will be completely anonymized.
- The central study database will comply with the highest safety standards according to ICH-GCP (see ICH, n.d.) (e.g., locked filed cabinets, secure storage for detachable media, protection of passwords, restrict group logins IDs, avoid using non-desc PCs or laptops for collection or storage of confidential research data, etc.) and will not include any information that could cause personal information, particularly name, address, telephone, and so forth, to be revealed. Access to data entered into the database will be permitted only for authorized personnel directly involved with the study and will be protected against unauthorized access according to the best industry standards of data security. Monitoring of data quality, quality assurance strategies, procedures for data lock, and cleaning will be performed according to the data management plan. If the participant withdraws a previously given informed consent or refuses to consent for continuation in the trial, the data will be handled as follows: data collected to the point of withdrawal of consent will be used as part of the intention-to-treat analysis. The sponsor ensures that investigators will permit trial-related monitoring, audits, institutional review board (IRB) review, and regulatory inspections, providing direct access to source data/documents.

Recruitment Process

Gender imbalance

It is important to analyse the participation rate of women in clinical trials.[4] In a recent article published in the *European Journal of Cardiology* (van Diemen et al., 2021), the authors identified and analysed the problem of the low representation of women in clinical trials, and they launched a call for attention. To better understand the factors that cause underrepresentation of women in clinical trials, the authors addressed through a literature review the challenges in enrolment: motivators, facilitators, and barriers to the enrolment and continuation of women in clinical trials.Motivators included the possibility of accessing better and continuous care. However, no study reported possible facilitators to improve the participation rates of women in trials.



As for the barriers, there were time limitations and fear of participating in clinical trials with an experimental design or the possibility of an unfavourable result. In addition, issues with transportation were reported more frequently as a reason for refusing participation in a trial. Women with a better socioeconomic position presented a greater willingness to participate and women with limited resources were underrepresented, generating greater inequity and disparity. In a similar way, it is important to collect information in research about gender identify and sexual orientation. Epidemiologically, there are several issues which disproportionally impact the LGBTQIA+ community, such as 40% higher use tobacco in people who identify as lesbian, gay, or bisexual than in people who identify as straight/heterosexual (see WCG ALIVE Employee Resource Group, n.d.), or a higher prevalence of depression and mood disorders compared to straight/heterosexual people.

[4] In the EU, see: European Medicines Agency, 2005; European Commission, 2013; European Commission, 2016.

Table 4

Recommendations to improve representation of women in clinical trials

Solutions	Description
Role of scientific journals and peer-reviewed media outlets	It is proposed as a simple and quickly applicable solution that all scientific journals require authors to address sex and gender differences to publish manuscripts.
Improvement in randomized controlled clinical trial design	It is a priority to investigate the motivators, facilitators, and barriers to participation in research and thus develop interventions that can promote the participation of women.
Increase diversity of the research team	One way to increase female participation rates would be through the implementation of a diverse research team. A diverse workforce is better able to understand diverse participant populations.
Developing sex and gendered educational curricula in medicine	Education that is responsive to gender and sex diversity needs to be designed and implemented to prepare medical students, residents, and researchers for a more diverse population of patients in the future.
Improving access to clinical trial sites	Improving access to sites participating in trials and facilitating logistics (on-site childcare or transportation) can help women increase their participation. Additionally, improving the comfort level and overall clinical trial experience from consent to use of biological samples could help them feel more comfortable.

Source: van Diemen et al., 2021.

- Regarding gender/sex aspects, the TTVGUIDE IT trial considers these aspects. The clinical trial is expected to be safe for both men and women, and differences in treatment effects between the sexes are unlikely.
- However, gender and sex dimensions are important factors in the project proposal and have been taken into account at various stages of the trial:

- At the trial design, the association between sex and TTV level, organ rejection and medical adherence was considered: female sex is associated with lower TTV levels and lower rates of rejection and nonadherence. Baseline variables and follow-up data known to be influenced by sex and gender will be collected. The study is designed as a mixed-sex study with equal sex distribution among the participants in order to reflect the composition of the group of patients likely to be treated with the strategy under investigation.
- At the analysis, data will be analysed separately for women and men and possible effect modifications will be considered. It would be recommendable to consider separately data analysis in the case of transgender or intersex participants. Likewise, factors that interact with sex/gender will be included. The study is not powered to analyse the outcome stratified for sex/gender as a subgroup.
- For dissemination, results will be displayed according to sex/gender and differences between the women and men will be reported. Implications for clinical practice or further research concerning sex/gender will be emphasized.

Governance

Clinical trials are the gold standard to develop an evidence-based biomedical practice. In addition to protecting the rights and interests of participants in clinical trials, research projects have to monitor that trials are conducted efficiently and lead to reliable results. Increasingly, research projects and clinical trials involve multiple research groups and investigators. Multinational consortia are formed, and this requires accommodation of different jurisdictions.

Governance is defined as the set of methods designed to ensure accountability, transparency, equity, stability, inclusiveness, empowerment, and participation of all stakeholders. Another way of understanding governance in the context of research and in particular clinical trials is to define it as a broad set of regulations, principles, and standards of good practice that exist to achieve and continuously improve the quality of research. It can be understood as a policy instrument that allows for better oversight of clinical trials.

- In this sense, the TTVGUIDE IT trial will manage the research process from the beginning of the clinical trial, its execution and up to the dissemination and exploitation of the research results. Of course, the TTV GUIDE TX project will be responsible for setting the appropriate standards for the best research.
- TTV GUIDE TX will be in charge of obtaining the necessary approvals for research work; improving the ethical and scientific quality of research; maintaining the safety of project investigators and third parties; ensuring high quality research procedures and practices; identifying potential avenues for research exploitation; reducing adverse incidents; ensuring that lessons are learned; and preventing misconduct and misbehaviour.
- By involving patients in the design of the communication tools about informed consent, this project fosters participation and stakeholders' empowerment. The ELSI study provides an opportunity for receiving feedback from both patients and professionals on the ethical and legal issues related to the study, which increases participation and helps to address equity issues, not only for the project but also for future clinical trial design. Transparency is fostered through the consortium website, which hosts detailed but accessible information related to the ELSI aspects of the study. Accountability is ensured through different methods, including this ethical and governance framework, and the participation of the Ethical and Governance Council as an independent forum.

Good Practices in Clinical Research

good practices in research and help prevent misconduct, in order to assist TTV GUIDE TX project's researchers to conduct research of the highest quality. It provides general principles and standards for good practice in research.

Researchers should adhere to the following principles, which aim to encourage all involved in research to consider the wider consequences of their work and to engage critically with the practical, ethical and intellectual challenges that are inherent in the conduct of high quality research.

The purpose of this section is to encourage

Table 5

Principles for the promotion of good practice in research

Principles	Description
Excellence	Excellence should be pursued when conducting research and aim to produce and disseminate work of the highest quality. Within the TTV GUIDE TX project, clinical research pursues the highest level of excellence.
Honesty	Researchers should be honest in relation to their own research and that of others. To ensure the accuracy of data and results, acknowledge the contributions of others, and neither engage in misconduct nor conceal it are the minimum requirements expected from researchers. The TTV GUIDE TX project aims to create and maintain a culture of research that fosters and supports honesty in research.
Integrity	Researchers must follow all legal and ethical requirements relevant to the research.[5] They should declare any potential or actual conflicts of interest relating to research and resolve them if necessary. Integrity is a core value of the TTV GUIDE TX project.
Cooperation	Researchers are encouraged to exchange ideas, research methods, data, and results, as well as their discussion, scrutiny, and debate. The cooperation within the TTV GUIDE TX project will always take place according to the respect for confidentiality.
Accountability	Accountability is equated with answerability, blameworthiness, liability, and the expectation of account-giving. Researchers within the TTV GUIDE TX project are accountable to the public and they should act accordingly. They should follow appropriate governance and transparency in their research, ensuring that any research undertaken complies with agreements, terms

[5] For "Integrity": ALLEA, 2017.

	and conditions relating to the project. Researchers also must follow the requirements and guidance of the body regulating their profession.
Training and skills	Organisations should provide training and opportunities for development for their researchers, and the necessary resources to enable them to conduct research to the required standards. They should support researchers in identifying unmet needs for training and development. The TTV GUIDE TX project should provide training and the necessary resources to enable the researchers to conduct research according to the required standards. The TTV GUIDE TX project will support researchers in identifying unmet needs for training and development. If the researchers identify unmet needs, they should report them.
Safety	Researchers should ensure the dignity, rights, safety, and wellbeing of research subjects, patients, participants, researchers, and others. They should avoid unreasonable risk or harm, as well as report and address any concerns relating to the dignity, rights, safety, and wellbeing of those involved in research. Research should be initiated and continued only if the anticipated benefits justify the risks involved. The TTV GUIDE TX project aims to demonstrate the safety and efficacy of TTV-guided immunosuppression in reducing infection and rejection. Thus, safety will be monitored in detail.

Source: Adapted from UK Research Integrity Office, https://ukrio.org/publications/code-of-practice-for-research/2-0-principles/

Interdisciplinarity

Interdisciplinarity, or collaboration across disciplines, is vital in clinical practice, and it is necessary to generate high-quality actionable research. Interdisciplinarity is founded on the premise that individuals have special areas of expertise and capabilities, and those can be shared with other partners to enhance their overall capacity for mutual benefit, to increase effectiveness, and to optimally align resources (VanWormer et al., 2012). Interdisciplinary research has the potential to improve communication and accelerate discoveries and their translation into practice. VanWormer et al. (2013) provide an overview of attributes of effective interdisciplinary collaboration:

Table 6

Charactersitic	Importance
Strong Working Relationships	Mutual appreciation of the individuals that work together motivates each team member to do a better job.
Shared Purpose	Working on agreed upon goals maximizes motivation and productivity of team members.

Charactersitic	Importance
Effective Conflict Resolution	Disagreement or conflict may be inevitable when undertaking complex tasks. Effective conflict resolution is necessary to maintain working relationships.
Adequate Time	Effective collaboration requires adequate time for all team-related tasks. Otherwise, conflicts may remain unresolved, the shared sense of purpose is diluted, and relationships drift.
Useable Technology	Complex technology may be underused, misused, or frustrate individuals when it does not work properly.
Role Clarity	Role clarity informs what needs to be done, who is responsible for doing it, and who is accountable if something goes wrong.
Cultural Respect	Respecting each other's backgrounds and experiences creates a comfortable interpersonal environment that facilitates a general sharing of ideas and constructive criticism.

The interdisciplinary research collaboration comprises diverse elements. Especially important are strong communication skills by the principal investigators and other team members across disciplines. An effort to develop strengths within the team and problem-solving for barriers to functional team dynamics may result in minimal disruption to the workflow and help achieve positive outcomes (VanWormer et al., 2013). Interdisciplinary research can produce better scientific contributions than those produced by any specific discipline alone. Interdisciplinary collaborations that fail to produce useful, efficient, creative, or meaningful outcomes raise questions of whether "collaboration" truly occurred and of what barriers or failures within the workgroup may have limited its achievement. The success of interdisciplinary collaboration can be assessed regarding the processes that are inherent within it and regarding the outcomes. An effective interdisciplinary collaboration provides a framework and means of creating a whole that exceeds the sum of its parts (VanWormer et al., 2013).

- For the TTV GUIDE TX project, interdisciplinarity is of paramount importance. Due to that, a consortium including the leading European investigators on TTV monitoring in the field of kidney transplantation was established for the TTV GUIDE TX project.
- Clinical virologists, transplant nephrologists, nephron-pathologists, infection specialists and biostatisticians are involved in the study design and conduction of the TTVGUIDE IT trial. In addition, an industry partner specialized in microbiological diagnostics (bioMérieux); an H2020 administration specialist; a public, the European Clinical Research Infrastructure Network (ECRIN), a non-profit organisation that links scientific partners and networks across Europe to facilitate multinational clinical research (https://ecrin.org/) and transplant ethics specialists have contributed to the project design.
- In addition, the clinical trial will involve 13 recruiting centres in Austria, Germany, the Netherlands, Spain, the Czech Republic and France. These are independent interdisciplinary service facilities to support clinical research in accordance with legal and ethical requirements. Clinical Trials Centers are involved in the administration of multinational multicentre trials. They provide support for physicians and scientists working in hospitals or outpatient units and partners from the pharmaceutical industry for the planning, conduct and analysis of clinical

research projects. Academic researchers and commercial sponsors profit from the centers' expertise in clinical trial monitoring, project management, regulatory affairs, data management, pharmacovigilance, and medical writing. Among the roles and responsibilities beyond supporting, facilitating and coordinating the day-to-day activities of the clinical trial, the Clinical Trials Coordinator Centers task is to survey the health status of the participants after the clinical trial has ended.

Checklists

A *checklist* is defined as a "list of action items, tasks, or behaviours arranged in a consistent manner, which allows the evaluator to record the presence or absence of the individual listed item" (Hales et al., 2008, p. 24). Checklists are effective tools because they have an impact on human performance. On the one hand, checklists help to compensate for multiple types of memory failures. Even when the type of errors vary with expertise, all human beings are susceptible to these failures regardless of their experience or seniority (Chaparro et al., 2019). Checklists have several benefits in clinical practice, such as serving as a memory aid by facilitating the recall of information from long-term memory, ameliorating the effects of stress, fatigue, and distraction that can interfere with retrieval of information from long-term memory, or enabling the clinician to identify and correct missed steps (Chaparro et al., 2019). Checklists help to standardize performance of tasks across users, which can ensure the adherence to accepted best practices.

The UK Research Integrity Office (UKRIO) recommends a checklist for researchers,[6] which lists the key points of good practice for a research project and is applicable to all subject areas. This checklist is divided into three parts: (a) Before conducting the research; (b) along the research; (c) at the end of the research. Using the checklist can help researchers and organizations meet the requirements of regulatory, funding and other agencies and ensure that important issues have not been overlooked.

We propose to take this checklist as a framework for researchers in the TTV GUIDE TX project, with special attention to the second and third sections.

[6] UKRIO Recommended Checklist for Researchers, available at: https://ukrio.org/publications/checklist-for-researchers

UKRIO RECOMMENDED CHECKLIST FOR RESEARCHERS

Before conducting your research, and bearing in mind that, subject to legal and ethical requirements, roles and contributions may change during the time span of the research:

- **1** Does the proposed research address pertinent question(s) and is it designed either to add to existing knowledge about the subject in question or to develop methods for research into it? ☐
- **2** Is your research design appropriate for the question(s) being asked? ☐
- **3** Will you have access to all necessary skills and resources to conduct the research? ☐
- **4** Have you conducted a risk assessment to determine: ☐
- **a** whether there are any ethical issues and whether ethics review is required; ☐
- **b** the potential for risks to the organisation, the research, or the health, safety and well-being of researchers and research participants; and ☐
- **c** what legal requirements govern the research? ☐
- **5** Will your research comply with all legal and ethical requirements and other applicable guidelines, including those from other organisations and/or countries if relevant? ☐
- **6** Will your research comply with all requirements of legislation and good practice relating to health and safety? ☐
- **7** Has your research undergone any necessary ethics review (see 4(a) above), especially if it involves animals, human participants, human material or personal data? ☐
- **8** Will your research comply with any monitoring and audit requirements? ☐
- **9** Are you in compliance with any contracts and financial guidelines relating to the project? ☐
- **10** Have you reached an agreement relating to intellectual property, publication and authorship? ☐
- **11** Have you reached an agreement relating to collaborative working, if applicable? ☐
- **12** Have you agreed the roles of researchers and responsibilities for management and supervision? ☐
- **13** Have all conflicts of interest relating to your research been identified, declared and addressed? ☐
- **14** Are you aware of the guidance from all applicable organisations on misconduct in research? ☐

When conducting your research: ☐

- **1** Are you following the agreed research design for the project? ☐
- **2** Have any changes to the agreed research design been reviewed and approved if applicable? ☐
- **3** Are you following best practice for the collection, storage and management of data? ☐
- **4** Are agreed roles and responsibilities for management and supervision being fulfilled? ☐
- **5** Is your research complying with any monitoring and audit requirements? ☐

When finishing your research: ☐

- **1** Will your research and its findings be reported accurately, honestly and within a reasonable time frame? ☐
- **2** Will all contributions to the research be acknowledged? ☐
- **3** Are agreements relating to intellectual property, publication and authorship being complied with? ☐
- **4** Will research data be retained in a secure and accessible form and for the required duration? ☐
- **5** Will your research comply with all legal, ethical and contractual requirements? ☐

In addition, the UKRIO provides a “Researcher Checklist of Ethics Applications for Research with Human Beings”, which is structured following the three elements of an ethical review: the application detailing the study and its ethics protocol, participant information including recruitment material, and the consent process. In this checklist, the researchers can assess the general issues that a research ethics committee may consider when reviewing an application (see UKRIO, 2020).

Communication Between Researchers, Participants, Stakeholders and the Public

Communication and cooperation in the research group

It is important to identify the areas of complementarity between the different members of the group, and establish communication channels and tools to promote interaction, mutual enrichment, and favour the development of capabilities. This cooperation will guarantee fair recognition of the work and results obtained by each of the members.

The members of the research group must maintain an honest, frank, open, and continuous communication that allows adequate understanding and interpretation of the research developed within the group. The members of the research group have the obligation to commit to the global objectives of the team and assume its responsibilities within it. This includes to (CSIC, 2011):

- actively participate in group coordination activities that include the definition of objectives, the discussion of results and making plans for the future;
- share their experience and actively participate in the advice and training of other colleagues;
- collaborate with other research groups belonging to the Institution or other entities; and
- not hinder the investigative work of competing groups or those with whom disputes are maintained.

Fostering cooperation within the research group and working in a team is one of the priorities of the TTV GUIDE TX project. During the 1st year of the project, three main meetings involving all partners were planned:

- Kick-Off meeting in May 2021
- M6 meeting Nov 2021
- M12 meeting in May 2022

Additionally, two training days as internal meetings involving the personal engaged in the clinical trial took place in March and April 2022.

Communication between researchers and participants

Transparent, clear and regular communication will be important to inform participants of general findings from research and to encourage continued participation. Therefore, TTV GUIDE TX project will look for a variety of ways for communicating with participants, as well as the public, research users and the scientific community. We stress that communication requires to pay special attention to listening to these stakeholders, and particularly listening to participants.

TTV GUIDE TX offers a variety of media to communicate with the public, which include the website (https://www.ttv-guide.eu/), patient folder about the trial, and public meetings. Those will be used to inform participants about the development and use of the resources, and will explain ways to

contact TTV GUIDE TX project's management. Communication with participants will include how to withdraw, for instance. TTV GUIDE TX project aims to explore how participants would like to receive and exchange such information. The project website provides information about different sections of the project. There is a section describing the team of principal investigators of the consortium comprising seven European countries. Two sections are dedicated to patients and health professionals. The section dedicated to patients explains the background of the project and how a Patient Advisory Board (PAB) has been set up to ensure that patients' needs are taken into account throughout the duration of the project.

Communication between researchers and stakeholders and the public

Stakeholders are individuals or collectivities who may be affected by the research. Stakeholders are usually patients, patients associations, and the public, including family members and concerned civil society. Patient and public involvement (PPI) in research has long been promoted in the UK and many other countries have made it compulsory.

PPI allows research to address patients' needs and perspectives and different voices to be part of the conversation for the best responsible research.

The TTV GUIDE TX project will establish appropriate channels of communication to promote PPI. A project website has been designed and launched (https://www.ttv-guide.eu/). The website includes press releases and information in separate sections for the general public and for patients, clinicians, and scientists. A FAQ section on the ethical and legal issues of the project has been included. An intranet project portal with a login area for partners will facilitate effective communication and knowledge management among the members of the consortium and the EGC (Ethics and Governance Council) and will also include an online reporting system to track project progress in the intranet. Each partner will link the website to their departmental/institutional websites and publish project news.

Patient Engagement

Although health research is carried out to produce knowledge that can ultimately lead to better treatments for patients, patients themselves are not always able to influence the setting of research priorities, research design, collaboration in research implementation, and so forth (Serrano-Aguilar, 2009). However, patient participation can contribute to increase the acceptability and accessibility of health services, as well as to improve both the quality and relevance of research (Caron-Flinterman et al., 2005; Bombard et al., 2018; Tomlinson et al., 2019). Patients contribute through their specific knowledge based on personal experience with the disease, symptoms, therapy, and the health system. This experiential knowledge can complement the knowledge of researchers by providing broader perspectives and other options (Entwistle et al., 1998; Caron-Flinterman et al., 2005). This aims to increase the relevance of health research, since it is possible that research questions that are relevant from a scientific perspective do not meet the expectations and needs of patients (Serrano-Aguilar et al., 2009).

Patient engagement is an increasingly important aspect of successful clinical trials. It can be defined as an effort to extend the benefits of patient insight and experiences, as well as desires and preferences, in research through collaborative relationships, in order to conduct more efficient and patient-centered, high-quality research (Patrick-Lake, 2018). There are various ways in which patients can be included in health research (Tomlinson et al., 2019): (a) work with existing patient groups; (b) form a patient advisory group; (c) consult with patients in outpatient clinics; or (d) use a panel of online patients.

- Patient engagement has been incorporated within the TTVGUIDE IT trial at the stage of trial design. The anticipated reduction in the burden caused by infectious disease is an important patient-centered outcome, as kidney transplant representatives have emphasized. Patients approved the specific measures developed to reduce participant risk during the trial, esteemed the fact that they do not need additional visits for the trial and the possibility of travel reimbursement. Patient engagement in the design of the clinical study would increase patients' compliance with the protocol.
- By the assistance and advice of a PAB, the TTV GUIDE TX project will involve patients throughout its duration thereby incorporating patients' needs and views throughout the project. The PAB will support patient-friendly developments in the healthcare sector and help take the views and needs of patients into account as much as possible throughout the project. As an example, WP2 will involve the PAB in the development of audio-visual materials for the website. WP2 will also carry out a sub-study to understand the ethical, social, and legal implications of the TTV GUIDE TX project, with feedback from both patients and professionals involved in the clinical trial.

Professional's Training

The ethical and scientific standard for the conduct and reporting of clinical trials involving human participants is known as Good Clinical Practice (GCP).Its main focus is the protection of the rights, integrity, and confidentiality of clinical trial participants, as well as the accuracy and scientific integrity of the data collected during clinical trials and reported in the results. Various regulatory agencies expect that clinical research personnel have an understanding of GCP prior to engaging in clinical research.

Most GCP training programs cover the following topics: institutional review board or independent ethics committee oversight, investigator responsibilities, staff training and delegation of responsibilities, protocol adherence, data management, informed consent, vulnerable populations, adverse event reporting, and site monitoring (Arango et al., 2016).

Participating principal investigators in the TTV GUIDE TX project have to provide a GCP certificate, which also includes training on the informed consent forms (ICF). As stated in the project proposal, and we quote verbatim:

"Treating physicians will receive in-depth training and detailed standard operating procedures on TTV-guided TAC dosing, including all common clinical scenarios, prior to the start of the interventional part of the trial".

Space for Discussion on Ethical Issues Related to the Research

Although the focus of an ethical framework for a clinical trial and project such as the TTV GUIDE TX project is to examine ethical issues of the research process in advance, emphasis should also be placed on welfare monitoring during the conduct of research. Therefore, whenever possible, discussion of ethical issues that may arise or doubts about the impact of the research should be facilitated among participants and sponsors of the project, as well as health professionals.

The ethical conduct of a clinical trial is not concluded after the formulation of the project, study design or even the signing of the informed consent. Patients' rights and interests must be protected throughout the duration of the project and even after its completion. It is important to create a professional relationship in which the researchers can ask questions and express their concerns regarding ethical issues within the research project.

In parallel to the clinical trial of the TTV GUIDE TX project, the researchers of the University of Granada (WP2 Ethics and Governance) will carry out a survey study in which they will ask professionals and participants about ethical issues that will allow them to understand in a qualitative way their experience during the development of the study.

Research Integrity Policy

Research integrity policy is essential for research that receives public funding. All research that is valued by society and that receives public funds are expected to maintain good research conduct and support research integrity (ALLEA, 2017).

As it could not be otherwise, the TTV GUIDE TX project is governed by a number of principles conducive to responsible research. Core elements of research integrity are: honesty; rigor; transparency and open communication; care and respect; and accountability. The research of the TTV GUIDE TX project is designed, reviewed, managed, and undertaken in a way that ensures integrity, quality, and transparency. In order to adhere to the objectives of research integrity, the project promotes safe and ethical research.

Some recommendations appear in the literature in relation to research integrity and that can prevent research misconduct and not jeopardize scientific practice. For example, beyond the issues of plagiarism, fabrication, or suppression of results, Shaw and Erren (2015) provide some specific recommendations to particular integrity issues. In the table below, we present their recommendations and brief definitions.

Table 7

Recommendations	Definition
All Papers Submitted Must Contain Contributorship Statements	Each author's contribution should be included to avoid ghost authors or dishonest attribution.
All Financial Conflict Of Interests (COIs) Must Be Reported with No Time Limits	Any existing conflict of interest must be declared.
Relevant, Non-financial Potential COIs Must Be Declared	In addition to monetary conflict of interests, other, sometimes more damaging, non-monetary conflicts of interests must also be declared.
Trials Must Be Reported Accurately, As Well As Registered	Trial registration is a condition of approval
Any Use of Metrics in Research Decisions Must Be Evidence Based	Avoid misuse of metrics because it could compromise the research processes.
All Breaches of Integrity Guidelines Should Be Punished or Remediated	Sanctions are to be implemented for those who break the rules of research integrity.
All Institutions Must Have Clear Procedures for Raising Concerns and Protections for Those Who Do So	All universities and research institutions must have clear pathways for raising concerns, protections for whistleblowers, defined punishments for wrongdoers, and strong powers for Research Integrity Officers (RIO).
Raising Concerns about Suspected Misconduct Must Be Mandatory	All integrity policies should mandate whistleblowing on integrity issues.
RIOs Must Have the Power to Enforce Integrity Policies	RIOs must have the power to initiate academic misconduct proceedings.
Integrity Policies Must Be Highly Visible and Understood	All researchers must be aware of any relevant institutional or national guidelines regarding research integrity.

Conflict of interest

Conflict of interest (COI) is understood as all those situations in which the judgment of a person in regard to the main interest of scientific knowledge is influenced by a secondary interest, such as financial, academic, political, or personal. One of the most common situations that can lead to conflicts of interest is associated precisely to relations with industry, where the results of clinical research may be conditioned by the commercial yields expected by the industry.

The activity of the clinician-researcher who experiments with his/her patients is subject to COI, since the role as a scientist is not always compatible with the duty as a doctor. The clinician-researcher must carefully separate these two roles: one as the provider to whom the patient comes to be treated in a ward, a clinic, and so on, and the other one as the researcher who may propose the patient to participate in a study. When requesting consent for biomedical research, the information on efficacy and safety is less precise, since the necessary knowledge about it will not have been acquired until the end of the research. It is important to clarify these elements to the patients (Rodríguez-Arias et al., 2008). There are other circumstances, not

so obvious, that can also lead to dubious ethical conduct and/or pretensions.

Therefore, researchers must pay attention not only to actual conflicts of interest, but also to potential ones and to those that are considered inappropriate acts from the perspective of good practices.

These include gifts from pharmaceutical companies to health professionals or the demands of confidentiality of the results that some promoters demand from researchers, delaying the dissemination of findings to society, for their own benefit.

Since COI can pose a threat to scientific integrity, the precautionary and preventive measure essential for its avoidance is the public declaration of the interests that may come into conflict.

Any real, apparent or potential COI must be declared, that could unduly influence or compromise the proper execution and development of scientific activity in its different dimensions, the protection and dissemination of its results and research management.

As part of the TTV GUIDE TX project, researchers should declare any potential or actual conflicts of interest relating to research and to withdraw professionals from decision board if necessary.

Dissemination of knowledge

For ethical conduct in research, the dissemination of knowledge, or the distribution of new knowledge gained through research, is essential. Particularly, when research is designed to improve health, dissemination is critical to the development of evidence-based medicine, as well as the adoption of evidence-supported interventions. All of them aim to improve practice patterns within specific settings. On the other hand, research may be considered a waste of resources and a useless pursuit unable to influence positive health outcomes if there is a lack of dissemination is lacking (Derman & Jaeger, 2018). Implementation research has produced many tools and strategies that can prompt more effective and timelier application of research findings to real world situations.

To maximize patient benefit, the main goal of the TTV GUIDE TX consortium is the rapid translation of TTV-guided immunosuppression to standard clinical practice. For this purpose, the dissemination strategies aim to:

- ensure full transparency of project activities, particularly with regard to ethical and regulatory issues; and
- enhance the visibility of the project and of European-funded research.

Dissemination is a key aspect to maximize the project's impact. Consequently, a plan for the dissemination of the project's results has been designed. The task leader for dissemination of the project results is the consortium coordinator Medical University of Vienna (MUW). Dissemination practices are incorporated as an own WP5 leaded by bioM with assistance of all involving partners, and all partners will be actively involved in the project's dissemination by using their existing networks, through which the project's objectives and results can be communicated at different levels, depending on the target groups:

- Scientific community, clinicians

- General public
- Patient's organizations/self-help groups
- Policymakers and regulatory authorities

The channels for communication about the results of the TTV GUIDE TX project with the main target groups are shown in Annex 1. The main routes for dissemination about the work and results of the TTV GUIDE TX project are shown in Annex 2.

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Annex

Annex 1

Table 8

Overview of the target audiences and channels for communication and dissemination

Audience targeted	Main objective	Channels/activities
Scientific community, clinicians	• Inform and create awareness about the potential of guidance of immunosuppressive therapy by TTV • Two-way communication regarding needs risks and experiences at conferences and events • Promote exploitation and transfer of results during the course of the project	• Presentations at national/international meetings/conferences of scientific associations • Publications in international scientific peer-reviewed journals, public website with a section specifically for the scientific community/clinicians • Networking with other relevant projects • Liaison with umbrella associations and related working groups
General public	• Provide understandable information regarding the objectives and results of TTV GUIDE TX • Ensuring full transparency of TTV GUIDE TX activities	• Public website presenting project activities • Electronic mass media • Press releases targeting the general press • Leaflet on the objectives and results of the project (print and digital version) • Events targeting non – specialists audiences • Harness EU-wide dissemination channels
Patient organisations/self-help groups	• Outreach to affected patients and their families • Create a two-way dialogue on needs, risks and experiences • Involve these groups in the dissemination of the objectives and the results of TTV GUIDE TX	• Linking the public website of TTV GUIDE TX to patient groups and independent European information platforms • Dialogue with patient forums • Leaflet on the objectives and results of the project (print and digital version) • Events/fairs targeting patients
Policy makers and regulatory authorities	• Raise awareness about the socioeconomic potential of the TTV R-GENE® assay • Promote reimbursement of the caregivers	• Direct personal contact and contacts via international and European associations • Involvement in expert advisory groups

Annex 2

Table 9

Selection of existing channels for communication and dissemination

Type	Participation
Scientific societies	**International** • European Society of Transplantation (ESOT) • European Renal Association/European Dialysis and Transplant Association (ERA-EDTA) • European Society of Clinical Virology (ESCV) • The Transplantation Society (TTS) • International Society of Nephrology (ISN) • American Society of Transplantation (AST) • American Society of Nephrology (ASN) • Ethical, Legal, and Psychosocial Aspects of Transplantation (ELPAT) **National** • Austrian Society for Transplantation, Transfusion and Genetics
International peer – reviewed scientific journals	• Trials • American Journal of Transplantation (AJT) • Journal of the American Society of Nephrology (JASN) • Transplantation • Journal of Virology • Clinical Infectious Disease
International and national projects	**International** • European Network for Collaboration on Kidney Exchange Programmes (ENCKEP) **National** • Initiative Green Ribbon
Patients organizations/foundations	**International** • The European Kidney Patients' Federation (EKPF) **National** • Die Arbeitsgemeinschaft Niere Österreich (ANÖ)