INFORMED CONSENT IN CLINICAL TRIALS FOR PRIMARY MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)

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FUNDING

This research was done as part of the DECODE project (Defining stratification of patients with C3 Glomerulopathies/immune complex-mediated glomerular diseases for better diagnosis and tailored treatment) funded by the ERAPerMed Joint Transnational Call 2020.

TO REFERENCE THIS REPORT

Budin-Ljøsne I, Carver RB, Logstein HS, Sand BW. "Informed consent in clinical trials for primary membranoproliferative glomerulonephritis (MPGN)". 2024, DECODE. ISBN: 978-82-8406-456-7

VERSION DATE

June 2024

Pictures on front page: shutterstock.com (Voyagerix, M. Novak)

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1. Introduction

1.1 What is MPGN?

MPGN stands for “Primary membranoproliferative glomerulonephritis” and represents a group of rare kidney disorders associated with complement activation [1]. In MPGN, there is an abnormal thickening of the glomerular basement membrane, which leads to impaired kidney function. The symptoms of MPGN can include blood or protein in the urine, high blood pressure, swelling in the legs or feet, decreased urine output, fatigue, edema, loss of appetite, anxiety and depression. MPGN is severe and the prognosis is unfavorable: about half of all patients, mostly children, develop end-stage renal disease and need dialysis within 10 years of onset.

Treating MPGN is challenging because of its heterogeneity. Patients have abnormal activation at different levels of the complement system. Historically, MPGN has been classified as type I, II and III based on light microscopy and glomerular ultrastructure. More recently, MPGN has been divided into different types of sub-diseases including IC-MPGN, C3 glomerulopathy (C3G), Dense deposit disease (DDD) and C3 glomerulonephritis (C3GN). However, this current classification brings challenges and does not fully reflect the disease etiology [2].

Treatment for MPGN depends on the type and severity of the disease and may include complement inhibitors, medications to control blood pressure, reduce inflammation, and suppress the immune system. In severe cases, kidney transplant may be necessary. It remains often unclear which patients are most likely to respond to a treatment [3].

Several drugs targeting the complement have been already approved or are investigated in trials for other conditions. Conducting clinical trials for MPGN patients is essential to identify new and more efficient treatment pathways.

1.2 The DECODE project

This guideline is developed as part of the DECODE project [4]. DECODE stands for *Defining stratification of patients with C3 Glomerulopathies/immune complex-mediated glomerular diseases for better diagnosis and tailored treatment*.

DECODE aims to improve the diagnosis and treatment of patients with C3 Glomerulopathies and other immune complex-mediated glomerular diseases. By combining the use of omics technologies and clustering analysis, the project develops a more precise and accurate method for diagnosing and classifying patients with these diseases based on their individual disease mechanisms. This involves identifying specific biomarkers, genetic mutations, and other factors that may contribute to the disease. Developing new methods for diagnosing and classifying patients may contribute to identify more tailored and personalized treatments for the patients. A primary outcome of the project will be the design of protocols for future clinical trials to evaluate the effect of selected complement inhibitors in patients stratified according to clusters. It is hoped that future clinical trials will offer patients a larger chance of recovery.

DECODE (2021-2024) is led by professor Ariela Benigni at the Mario Negri Institute for Pharmacological Research [5] in Bergamo, Italy, and involves partner research institutions from Italy, Greece, Germany and Norway as well as patient organizations in Italy and the Netherlands.

1.3 About this guideline

This guideline aims to provide comprehensive and tailored guidance regarding which information to provide to potential participants in multi-site clinical trials for MPGN under the informed consent process. The guideline is relevant for researchers, patient representatives and other stakeholders involved in the planning and conduct of clinical trials for MPGN.

The guideline was developed following several steps. Frist, we conducted a review of 1) legal requirements within the European Union (EU) concerning informed consent, 2) European and international ethical guidelines for health research, 3) recent scientific literature discussing informed consent and rare diseases, and 4) other relevant publicly available reports and guidance documents on informed consent. Main information elements from these sources were extracted to inform the development of this guideline. Second, we incorporated in the document the preferences of MPGN patients regarding information needs as reported in a consultation conducted by the DECODE project through a digital anonymous questionnaire and interviews [6]. To further inform the development of this guideline, a workshop was conducted with clinicians, researchers and patient representatives in September 2023 to review the draft guideline and discuss its future development. The draft guideline was shared with DECODE partners in March 2024 for final approval.

This guideline first provides an overview of the ethical and legal landscape for informed consent in clinical trials and a description of key features of the informed consent process. Then, it includes a description of the information to provide to adult clinical trial participants as well as young people aged 12 to 18 years, and a glossary of terms.

1.4 Informed consent in clinical trials

Obtaining the informed consent of potential participants in clinical trials is a central ethical and legal requirement. Informed consent aims to protect the individual's freedom of choice and show respect and concern for his/her rights, autonomy, and welfare [7]. It also aims to ensure that the individual has a comprehensive understanding of the trial objectives, procedures, potential risks and benefits, is aware of his/her rights as a research participant and can make an informed and voluntary choice about whether to participate in a research study [8] . Finally, the informed consent is a process to ensure the legal use of data sources according to the **General Data Protection Regulation (GDPR) [9].**

Three critical elements are required for an ethically valid and informed consent to participation in a clinical trial:

- **Voluntarism**: The ability of an individual to judge, freely, independently, and in the absence of coercion, what is good, right, and best subjected to his/her own situation, values, and prior history.
- **Decision-making capacity**: The ability to understand and appreciate the nature and consequences of health decisions and to formulate and communicate decisions concerning health care.
- **Information disclosure**: Providing information that is necessary for an individual to make an informed decision.

This guideline focuses on the **information disclosure**. By emphasizing the importance of providing information to potential participants, we aim to:

- Safeguard the rights and welfare of participants by ensuring they have a full understanding of the nature, purpose, risks, and potential benefits of the clinical trial.

- Enhance transparency and communication between researchers and participants, fostering trust and cooperation throughout the study.
- Promote ethical conduct and compliance with relevant regulatory and ethical standards, including the Clinical Trials Regulation (CTR) [10] and the General Data Protection Regulation (GDPR) [9].

2. The European legal and ethical framework for informed consent

In the EU, the legal requirements for informed consent in clinical research are governed by several regulations and guidelines, including the **General Data Protection Regulation (GDPR)** [9] (No. 679/2016) and the **Clinical Trials Regulation** (CTR) [10].

2.1 The General Data Protection Regulation (GDPR)

The GDPR is legally binding in the 27 EU member states and in the three additional European Economic Area (EEA) countries, those being Norway, Iceland and Liechtenstein. The GDPR sets out the rules for processing personal data, including personal data collected for clinical research purposes. The GDPR emphasizes transparency, fairness, and accountability in data processing activities and provides individuals with rights regarding their personal data.

For the processing of personal data to be legal according to the GDPR, a legal basis is required (GDPR Article 6). For scientific research, there are two potential legal bases:

- Informed consent: In the GDPR, informed consent is defined as*:" any freely given, specific, informed and unambiguous indication of the data subject's wishes by which he or she, by a statement or by a clear affirmative action, signifies agreement to the processing of personal data relating to him or her"*. [Art 4] [9]. The requirement for informed consent under the GDPR is very strict and stricter than in some national rules. The minimum information that must be provided for the informed consent to be valid includes details about the data controller's identity (e.g., the institution leading the clinical trial), the purpose of each processing operation, the types of data being processed, the right to withdraw consent, information about the use of data for automated decision-making, and any risks related to data transfers. The processing of special categories of data, such as health information, is generally prohibited but can still be carried out under Article 9 based on explicit consent, among other legal grounds [9].

In the GDPR, it is acknowledged that it is often not possible to fully identify the purposes of the processing of personal data at the time of collection of the information when scientific research is conducted. It is therefore seen as acceptable that research participants (data subjects in the GDPR) consent to specific areas within scientific research when this aligns with recognized ethical standards for scientific research.

- Public interest: This legal basis can be applied to research projects that are extensive, are expected to last over a long period of time, and in which obtaining comprehensive informed consent at the outset of the project is challenging. If this legal basis is employed, an additional legal basis in the European Union law or national law is also required. Using the public interest as a legal basis under the GDPR does not imply the omission of obtaining informed consent.

The European Data Protection Board has provided guidelines regarding informed consent, Guidelines 05/2020 on consent under Regulation 2016/679. In these guidelines the requirements for consent in the GDPR are specified, and examples are provided.

2.2 The Clinical Trials Regulation (CTR)

The Clinical Trials Regulation (CTR) replaces the existing Directive 2001/20/EC and came into application in the EU on 31 January 2022 with a three-year transition period. The aim of CTR is to harmonize the rules for assessment and supervision of clinical trials in the EU and EEA countries. Under the CTR, informed consent is described as *"a subject's free and voluntary expression of his or her willingness to participate in a particular clinical trial, after having been informed of all aspects of the clinical trial that are relevant to the subject's decision to participate or, in case of minors and of incapacitated subjects, an authorisation or agreement from their legally designated representative to include them in the clinical trial."* [10]

Under the CTR, informed consent aims to address ethical requirements originating from the World Medical Association (WMA) Declaration of Helsinki [8] and is not regarded as a tool primarily designed for adhering to data protection regulations. Distinction should therefore be made between collecting the consent of trial participants to data processing (as required in the GDPR) and consent to participation in research (as required in the CTR). Both requirements should be addressed during the informed consent process [11].

In the CTR, there are several requirements to the informed consent that must be met, such as ensuring that it is possible for the clinical trial participant to fully understand the nature, objectives, benefits, implications, risks and inconveniences of the trial and be aware of the right to refuse to participate og withdraw without any reason. Additionally, information must be provided about the expected duration of the participant's involvement in the trial, possible treatment alternatives, compensation options, communication channels for study results disclosure, and follow-up procedures if participation is discontinued. A qualified person should deliver the information through a pre-interview, using language understandable to a layperson, and providing information in writing. Confirmation of the participant's understanding should be obtained, and adequate time must be given for the participant to decide about participation in the clinical trial.

It is important to note that the legal requirements for informed consent may vary among European states, which can enact own national legislation based on the EU regulations. For instance, any EU country can decide to have specific national requirements for the collection of informed consent from minors, or the types of qualification the person conducting the pre-interview should possess. Researchers and sponsors should consult the specific regulations and guidelines applicable in the country where the research is conducted to ensure compliance with local requirements.

2.3 Other relevant legal framework

In addition to the GDPR and the CTR, the Oviedo Convention[1] outlines core principles of relevance for the informed consent process. The Convention is the first legally-binding international text that sets out rules related to medical research by including detailed and precise conditions, especially for people who cannot give their consent [12]. Importantly, The Convention asserts that every patient has the entitlement to receive information about own health, including the findings from predictive genetic tests. Additionally, the Convention acknowledges the patient's right to choose not to be informed.

2.3 Ethical guidelines

Several European and international ethical guidelines describe how the informed consent should be designed, organized and the type of information to provide to potential clinical trial participants:

- **The World Medical Association (WMA) Declaration of Helsinki** outlines ethical principles for medical research involving human subjects, including principles of respect for persons, beneficence and justice, the right to make informed decisions, and the recognition that some groups are vulnerable and require specific protection [8].
- **The 2016 International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS)** include a list of specific information points to provide to potential research participants [7].
- **The European Medicines Agency Guideline for good clinical practice E6(R2)** provide an international quality standard for conducting, recording and reporting trials that involve the participation of human subjects [13]. It includes an overview of essential documents for the conduct of clinical trials.

Other guidelines provide useful information about the informed consent process and content, e.g., the guidelines for tailoring the informed consent process in clinical studied developed by the I-consent consortium [14].

2.4 Participation of minors in clinical trials

Historically, it has been considered unethical to conduct research on, among other groups, minors. For safety reasons, minors have often been excluded from clinical trials for MPGN. This is however changing, and several ongoing clinical trials are recruiting children aged 12 and above as a recognition that children, too, deserve the opportunity to benefit from the latest medical developments. This is particularly important in MPGN as the disease appears in early age.

The GDPR and the CTR emphasizes that children (and their personal information) deserve special protection. A series of requirements are outlined that must all be met to include minors in clinical trials. The trials should aim to investigate the treatment of conditions that occur in children and must be focusing on a medical condition that affects them. Participation of children in clinical trials should provide a direct benefit to them or children in general, that outweighs potential disadvantages, and such disadvantages should be minimal. Information provided to children must be formulated in clear and simple language that the child can easily understand, must be tailored to the child's age and

[1] Council of Europe. Convention for the protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (ETS No. 164): Full list - Treaty Office (coe.int)

maturity, and delivered by someone with knowledge or experience of working with children. The child or adolescent should be given the opportunity to be involved in the actual decision-making process regarding participation [7]. Any explicit refusal from the child to participate in the clinical trial should be respected. Additionally, no financial benefits or other incentives beyond compensation for expenses should be provided.

The general rules for informed consent as described in this guideline also apply to minors. However, a clinical trial with minors can only be conducted if a parent or a legally authorized representative of the child or adolescent has given permission and the assent of the child or adolescent has been obtained. The assent is the affirmative agreement or willingness expressed by a minor to participate in a clinical trial. Like informed consent from adults, assent should be seen a process [7]. The age of assent from a child may vary from country to country. When a minor reaches the age where they can independently consent according to national legislation, explicit informed consent must be obtained before further participation in the clinical trial [10].

It is preferable to obtain assent from the minor in writing, if possible [13]. A few international ethical guidelines provide recommendations for how to design the assent process with minors. The "Assent / Informed Consent Guidance for Pediatric Clinical Trials with Medicinal Products in Europe" developed by Enpr-EMA's Working Group on Ethics [15] provides a useful list of assent/consent elements and ideas for how to formulate information points in a way that is understandable and relevant for young people.

It is important to note that since specific requirements and regulations for providing information to minors in clinical trials may vary by country or jurisdiction, it is recommended to consult with ethics committees, institutional review boards, or regulatory authorities to ensure compliance with local regulations and ethical standards.

3. Key features of the informed consent process

Informed consent should be seen as a *"process of informing and sharing information and addressing questions and concerns, rather than simply obtaining a signature on a prescribed form"*[7].

An ethically robust informed consent process should include the following features[2,3,4,5]:

- The informed consent of the individual must be obtained prior to clinical trial participation. If the individual is not capable of giving informed consent, the consent of the individual's legal representative should be obtained. When minors are invited to participate in clinical trial, their agreement (assent) to participation should be sought.

- Information given to the individual is concise, clear, relevant, comprehensive, as non-technical as possible, understandable to a layperson and tailored to the individual's age and capabilities.

[2] 2016 International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS)
[3] European Medicines Agency Guideline for good clinical practice E6(R2)
[4] Enpr-EMA's Working Group on Ethics. Assent / Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe
[5] I-Consent Guidelines For Tailoring The Informed Consent Process in Clinical Studies

- Information is provided to the individual in writing, e.g., leaflets. The use of technical innovations such as audio-visuals, infographics, pictures, drawings, cartoons, summary tables, graphic representation of the trial and glossaries may enhance comprehension and facilitate the individual's experience.

- The individual must be given sufficient time to reflect upon participation, consult family members or others, and ask questions, before reaching a decision.

- The person collecting the consent has made every effort to ensure that the individual understands what participation in the trial entails and is aware of the right to withdraw at any time and without consequences. Any decision to participate in the clinical trial must be free, voluntary and made without undue coercion or influence.

- The informed consent should be documented in writing, and the informed consent document signed and dated by the individual or his/her legal representative as well as the person conducting the informed consent process. A copy of the informed consent document should be provided to the individual or his/her legal representative.

- The informed consent of the individual must be sought again if substantive changes take place in the clinical trial (e.g., new risks and benefits) to enable him/her to re-evaluate participation or withdraw.

- Children participating in clinical trials should be asked for their informed consent to continue participation when they reach majority, including consent to the continued storage and use of their biological material and related data.

- If a minor refuses to participate or continue in a clinical trial, his/her decision should be respected, unless participation in the trial is considered in his/her best interest and risks and burdens are minimal.

- The person obtaining consent must be duly qualified and have prior experience in obtaining consent.

- Involving patients and patient advocacy groups in the design of clinical trial protocols and information material may be considered to ensure that the informed consent process and consent materials are understandable for potential participants and address their needs and preferences.

- The use of online platforms may be considered to facilitate regular interaction between clinical trials participants and researchers and build trust.

- It may be worth considering collecting a separate assent form minors for the conduct of genetic testing (to allow for sufficient time to explain the scientific reason, rationale, and procedures for giving test results, e.g., with help from a genetic counsellor, and for the collection of biological samples.

4. Dynamic consent

The information to provide during the informed consent process in an information sheet is often lengthy and can be seen by potential participants as overwhelming. There is a risk that patients do not

read the information provided and this can potentially lead to misunderstandings, unrealistic expectations or breaches of trust. Informed consent should also support continuous communication between trial participants and researchers. Dynamic consent has been proposed to facilitate two-way, ongoing communication between researchers and research participants. It usually consists of an online platform, such as an online portal or a mobile application [16].

Using the platform, researchers can easily update participants about the progress of the study, study results and changes to the protocol. Requests can be sent to participants, e.g., to ask additional questions or invite to consent to participation in new projects. Participants can access an overview of what they have consented to, manage their consent preferences, review updates and raise questions.

Researchers should consider implementing dynamic consent solutions in clinical trials for MPGN to promote transparency and exchange. The platform should be built in a way that secures the privacy and confidentiality of the participants' data. Efforts should be made to make the platform accessible to participants with varying levels of digital literacy and different abilities. Maintaining paper-based solutions in parallel may be necessary to address the needs of participants with varying ability or willingness to use digital platforms. In any case, the use of dynamic consent platforms should not fully replace face-to-face interactions between trial participants and the research team, which remain important to build relationships of trust.

It should be noted that not all European countries consider the use of electronic signatures as valid consent, and researchers should check which regulations apply locally at the clinical trial sites [11].

Example: The RUDY study is a study in rare diseases affecting of bone, joints and blood vessels, led by research team at the University of Oxford. It has developed a dynamic consent platform to support patient-driven research: https://www.rudystudy.org/

For the development of a dynamic consent platform, consult the European Medicines Agency "Guideline on Computerised Systems and Electronic Data in Clinical Trials – Draft"(2021).

5. What type of information do MPGN patients want?

In 2023, the DECODE project conducted a study to investigate the views and perspectives of an international sample of patients diagnosed with MPGN, and parents of children diagnosed with MPGN, regarding potential future participation in clinical trials. The study called IMPACT *("Identifying the perspectives of patients diagnosed with primary membranoproliferative glomerulonephritis and/or parents of patients regarding potential participation in future clinical trials"*) consisted of two steps: 1) an anonymous online survey with an international sample of MPGN patients/parents of minor patients and 2) digital interviews with MPGN patients or parents of minor patients. Survey results are available on the DECODE website [6]. The IMPACT study showed that patients would need the following information when considering whether to participate in clinical trials:

Trial design and practical aspects

- The objectives, rationale and procedures of the trial.
- The mechanism of action of the experimental drug and preclinical predictors of likely efficacy.
- The size of the placebo arm and information about expected disease progress, if the participant is placed in a placebo group.

- Whether the trial is accessible to transplant recipients and information about potential risks to a transplanted kidney.
- How participation in the trial can be combined with working obligations.
- Contact information of practitioner, nephrologist and/or patient organization that may help support the decision-making process.

Other practical aspects considered of importance included the number of biopsies to undergo, the frequency and number of visits to the hospital or research centre required, information about trial location and duration and any requirements to reduce current therapy.

Information about potential benefits and risks

Most study respondents wanted to receive information about the types of side effects the experimental treatment may have. Main motivating factors for entering a clinical trial were the hope that the new treatment will improve kidney function, the possibility to contribute to increased knowledge about the disease and experiencing a worsening of own current condition. This highlights the importance of providing information about the expected impact of the experimental drug on kidney function and the expected new knowledge to be gained from conducting the clinical trial.

General and individual clinical trial results

Most study respondents wanted to be informed about their or their child's individual results from a clinical trial as well as general trial results. Having the possibility to continue treatment for free after trial end was considered very important. It may be useful during the informed consent process to provide information about plans to provide general and individual results from the clinical trial to participants. If there are such plans, information about how the feedback process will be performed should be provided. Whenever possible, information about access (or no access) to the tested treatment after trial should also be provided. The IMPACT study participants also suggested providing information about results from previous trials, if relevant.

Data sharing and data privacy

Most study respondents wanted to know with whom their or their child's data is shared and for which purposes, including if used for commercial purposes. It may be useful during the informed consent process to provide information about data sharing plans, including how the data will be shared, with whom and for which purposes.

6. Characteristics of clinical trials for MPGN

Conducting randomized controlled trials (RCT) in the same way as normally done in common diseases is difficult for MPGN because of the low prevalence of the disease. Gathering enough patients for a RCT is difficult, and it is difficult to achieve statistical power and reliable results if there are two few patients in the trial.

MPGN is very heterogenous and not the same in every person, so testing new treatments may be complicated. Some drugs might only work for certain groups of people with MPGN, and their overall impact might be unclear. In future clinical trials, patients will have to be stratified according to clusters, i.e., patients will be grouped or sorted based on certain characteristics or features they share. Instead of treating all patients the same way, patients will likely be organized into clusters or groups that have similar traits or conditions.

Future Phase II clinical trials for MPGN will likely be organized in clusters. As is usual following phase I of a clinical trial that is designed to assess the safety of a new drug or treatment and determine the appropriate dosage, in phase II, treatment is extended to a larger number of patients to assess the efficacy of the drug in treating a particular medical condition. It is foreseen that the following clinical trial designs will be relevant for MPGN:

OFF(Baseline)-ON-OFF-ON-OFF clinical trial design

If less than 10 patients are included in the trial, the OFF(Baseline)-ON-OFF-ON-OFF clinical trial design may be preferred. This design involves patients receiving two active treatment periods that are compared with two placebo treatment periods:

- 12-week complement inhibitor treatment followed by 12-week of placebo, then 12-week complement inhibitor treatment followed by 12-week of placebo.

In total, the trial lasts 48 weeks.

Randomized cross-over clinical trials

If at least 10 patients (but less than 20) are included in the trial, the randomized cross-over design may be preferred. This design involves patients randomly getting two different sequences of treatments:

- One with a six-month complement inhibitor treatment followed by six months of placebo,
- One with six months of placebo followed by six months of complement inhibitor therapy.

This design enables to compare the six-month complement inhibitor treatment with six-month placebo and compare their overall effects. In total, the trial lasts 12 months.

Randomized trials with double-blind phase and open extension phase

If at least twenty patients are included in the trial, a randomized trial with double-blind phase and open extension phase may be preferred. The trial would include 2 phases:

- A six-month randomized, double-blind treatment phase where some patients get a complement inhibitor treatment, and others get a placebo, followed by

- A six-month open extension phase with all participants receiving the treatment.

This design would allow to compare the complement inhibitor treatment with a placebo, assess the outcomes over time within each patient, and compare the effectiveness of different treatment durations. In total, the trial lasts 12 months.

All study designs will likely require several biopsies (e.g., at inclusion, at six months and 12 months) as well as data on proteinuria, GFR/RPF and complement components/activity, which may be needed at regular intervals (every 2-3 months). Such data are usually collected through urine and blood samples. GFR and RPF measurements provide important information about the amount of blood the kidneys receive from the heart and how it is filtered and purified by the kidneys. Their measurement requires the intravenous injections of two substances (that are safe and well tolerated) and some blood sample collections after the infusion to evaluate how these substances are progressively eliminated from the circulating blood by the kidneys.

7. Essential information to provide during the informed consent process

The information elements to provide to potential clinical trial participants can be organized in four broad categories: 1) information about the research study, 2) information about data uses and protection, 3) information about participants' rights, and 4) other general information. The list below builds upon information elements provided in international ethics guidelines[6,7,8], elements of consent recommended by experts in rare disease research, and information needs expressed by MPGN patients. It aims to represent the highest legal and ethical standards applicable in the field and is tailored to the context of clinical trials for MPGN.

7.1 Information about the research study

7.1.1 Study aims and purposes

- Nature of the study (e.g., research), aims, how the research differs from routine medical care[6] and a description og aspects of the trial that are experimental[7]
- Mechanism of action of the experimental drug and preclinical predictors of likely efficacy *(wish of patients)*
- Trial design (e.g., randomization, double blinding, grouping of participants based on specific characteristics or biomarkers, expected number/proportion of participants in the placebo arm), and consequences of design (e.g., participant will not be told of the assigned treatment until the study is completed and the blind is broken) [6,7]

7.1.2 Reasons for participation

- Inclusion and exclusion criteria[8] (e.g., exclusion of pregnant women), estimated number of trial participants[6,7] and duration of participation[6]
- Whether the trial is accessible to kidney transplant recipients *(wish of patients)*
- Possibility of early termination of the trial [6,7,8]

7.1.3 Voluntariness of participation

[6] 2016 International Ethical Guidelines for Health-related Research Involving Humans of the Council for International Organizations of Medical Sciences (CIOMS)
[7] European Medicines Agency Guideline for good clinical practice E6(R2)
[8] I-Consent Guidelines For Tailoring The Informed Consent Process in Clinical Studies

- Voluntariness of participation and possibility to withdraw at any time without stating any reason and without penalty or loss of benefits[6,7,8]

7.1.4 Implications of participation

- Methods and procedures to be carried out by the research team and the participant, including number and frequency of invasive procedures (e.g., blood draws, kidney biopsies, electrocardiograms) [6,7,8]

- Trial locations, expected number and duration of visits to the research centre, total time involved and possibility to combine trial participation with working obligations[6,7,8]

- Consequences of participation for current treatment (e.g., whether current treatment must be upheld or reduced, limitations in the use of other medicines and natural remedies) [6,7,8]

- Planned genetic testing and description of the type of genetic analysis, e.g., one or several genes vs. more comprehensive mapping of the genome[7,8]

- Procedures for the collection of Patient Reported Outcomes Measures – PROMs (if applicable)

7.1.5 Risks and benefits of participation

- Foreseeable risks including side effects, inconveniences, pain and discomfort of experimental interventions (e.g., infections, swelling or pain at the infusion site, allergic reactions, risks related to kidney biopsy, risks to patients with a transplanted kidney), including risks to the health or well-being of the participant's direct relatives[6,7]

- Potential risks to women in child-bearing age, including potential consequences on pregnancy, the possibility to use contraception (if applicable), and procedures if the participant becomes pregnant during the study[6,7]

- Expected impact of the experimental drug on kidney function, on disease progress if the participant is placed in a placebo group, and expected new knowledge to be gained from conducting the clinical trial *(wish of patients)*

- Procedures to minimize risks and maximize benefits[6,8]

- Potential clinical benefits, if any, expected to result to participants from participating in the research[6]. Clear statement about no benefits if not expected[6,7] or if only general benefits are expected (e.g., benefits of the research to the community or to society at large, contribution to scientific knowledge).

7.1.6 Alternatives to participation

- Possibility of receiving standard treatment if the individual does not wish to participate in the study, including treatments or tests available in other regions/countries[8]

- Follow-up measures if trial participation is discontinued, and potential benefits and risks[7]

7.1.7 Costs and compensation mechanisms

- Anticipated expenses, if any, related to participation in the trial (e.g., travel costs) [7]

- Monetary or other forms of compensation for participation in the trial, frequency, and scheduling[6,7]

- Compensation and/or treatment available in the event of trial-related injury, nature and duration of treatment and limits of compensation, including information about the applicable damage compensation system and compensation in case of disability or death resulting from injury (if applicable) [6,7]

7.2. Information about data uses and protection

7.2.1 Use of biological samples and data

- Types of personal data collected and stored, linkages to other personal data or use of registries, data processing purposes and legal basis for the processing[6,7]

- Data sharing plans (e.g., which data will be shared with whom for which purposes), including transfer of personal data to countries outside of the GPDR jurisdiction, international organizations or commercial actors[7]

- Possibility that auditors, ethics committees or regulatory authorities may access personal data, e.g., medical records, for verification purposes[7]

- Possibility that some data may be hosted in open research databases (e.g., the European Genome-phenome Archive) *(Gainotti and al, 2016[9])*

- Name of the institution and project manager responsible for the processing of personal data[7]

- **If biological samples are stored in a biobank**: purpose of the biobank, conditions and duration of storage, rules of access to the biobank and data sharing plans, the right to withdraw and request destruction of samples and contact information, and procedures for the management of incidental findings.[6]

[9] Gainotti S, Turner C, Woods S, Kole A, McCormack P, Lochmüller H, Riess O, Straub V, Posada M, Taruscio D, Mascalzoni D. Improving the informed consent process in international collaborative rare disease research: effective consent for effective research. Eur J Hum Genet. 2016 Aug;24(9):1248-54. doi: 10.1038/ejhg.2016.2. Epub 2016 Feb 10. PMID: 26860059; PMCID: PMC4989211.

7.2.2 Data protection

- Measures to protect the privacy of participants and the confidentiality of their data, including genetic data[6]
- Possibility of experiencing breaches of confidentiality, and potential consequences[6] and limits to the research team's ability to safeguard confidentiality (e.g., impossibility to fully anonymize genetic information)
- Procedures for monitoring data sharing, e.g., involvement of an ethics committee or a data sharing committee (*Courbier and al, 2019[10]*)
- Possibility of being asked to provide new consent in the case of extended data sharing plans *(Gainotti and al, 2016[9]; Courbier and al[10])*
- Publication of clinical trial results without compromising the anonymity of participants[7]

7.3 Information about participants' rights

7.3.1 Information about general clinical trial results

- Procedures for informing participants clinical trial results (e.g., website, newsletter, email, or through ClinicalTrials.gov, and expected frequency of updates[11]

7.3.2 Information about individual clinical trial results

- Procedures to inform participants about individual clinical trial results (e.g., clinically actionable results), including genetic counselling and involvement of health care services[6]
- Reasons for not disclosing individual results, if applicable (e.g., if the research ethics committee does not approve disclosure) [6] *(Gainotti and al, 2016[9])*
- Possibility to ask for permission to access own genetic sequencing data, if applicable *(Gainotti and al, 2016[9])*

[10] Courbier S, Dimond R, Bros-Facer V. Share and protect our health data: an evidence based approach to rare disease patients' perspectives on data sharing and data protection - quantitative survey and recommendations. Orphanet J Rare Dis. 2019 Jul 12;14(1):175. doi: 10.1186/s13023-019-1123-4. PMID: 31300010; PMCID: PMC6625078.

[11] World Medical Association (WMA) Declaration of Helsinki (2022)

7.3.3 Post-trial access to treatment

- Possibility (or not) to access treatment identified as beneficial in the trial after trial end, and at which cost, if any[6,11]

- Potential risks if continued access to treatment is provided before regulatory approval[6]

7.3.4 Participant engagement

- Procedures to consult trial participants or participant representatives on the quality, detail and clarity of the information provided before the clinical trial starts *(Gainotti and al, 2016[9])*

7.3.5 Other rights

Clinical trial participants should be informed that they have the following rights:

- **Right of access:** The right to obtain confirmation on whether personal data are being processed and, if it is the case, the right to obtain access to personal data and related information (Article 15 GDPR). Information about procedures for requesting access (e.g., using a Data Access Request Form on the clinical trial's website) and how much time it normally takes to receive a response.

- **Right to rectification:** The right to request rectification of personal data, the correction of errors and the updating of incomplete information (by providing an additional declaration) (Article 16 GDPR).

- **Right to erasure:** Also known as "the right to be forgotten". The right to obtain the erasure of personal data without undue delay (Article 17 GDPR). The right is not absolute and follows certain conditions.

- **Right to restrict data processing:** The right to obtain a processing restriction from the Data Controller (Article 18 GDPR) under certain conditions.

- **Right to object:** The right to object to the processing of personal data (Article 21 GDPR) unless the processing is required for the performance of a public interest task pursuant to Article 89 of the GDPR.

- **Right to Data Portability:** The right to require that personal data (e.g., a data file in a readable format) are sent to the participant or to a third party (Article 20).

- **Right to withdraw consent to data processes:** The right to withdraw consent to data processes at any time. Data already collected and processed before withdrawal, and anonymous data, can still be used for research purposes.

- **Possibility to lodge a complaint:** The participants can lodge a complaint with a supervisory authority (e.g., the European Personal Data Protection Authority) in the case of violation of

fundamental rights and freedoms of participants in relation to the processing of their personal data.

7.4 Other general information

- Sponsors and sources of funding for the clinical trial, institutional affiliation of investigator(s), name of researchers, hospital/institution[7]
- Potential conflicts of interest and procedures to address these[7,8]
- Name of the research ethics committee that approved the research protocol and procedures to manage potential protocol violations[7]. *A copy of the ethics committee approval should also be made available to potential participants*[8].
- Contact information of practitioner, nephrologist and/or patient organization that can help potential trial participants during the decision-making process *(wish of patients)*
- Contact information for further information about the trial[7]
- Contact information of the institution's Data Protection Officer[7]
- Trial registration number[7]
- Permission to re-contact in the case of unexpected events to be addressed in the future *(Gainotti and al, 2016[9])*

8. Information elements to provide to minors

In principle, minors aged 12 or above can receive the same information as adults before considering participating in clinical trials, given that it is provided in a concise, transparent, intelligible, and easily accessible form, using clear and plain language. **Researchers may also consider providing information that is specific to this age group**:

- Information about why the clinical trial involves minors and how the trial relates to a medical condition from which the minor suffers or if of such a nature that it can only be carried out on minors
- Possibility for older adolescents to have a private conversation (without parents) with the trial staff about confidential / sensitive issues[12]

[12] Enpr-EMA's Working Group on Ethics. Assent / Informed Consent Guidance for Paediatric Clinical Trials with Medicinal Products in Europe

- If the trial involves missed school days, provide information on how educational support will be provided to ensure minimal disruption to the minor's education.

9. Participant involvement in clinical trials

Regulatory bodies and funding agencies increasingly recognize the value of patient input in trial design. MPGN patients and their families can help shaping several aspects of clinical trials. For instance, they can contribute to:

- The design of the informed consent process and content to ensure that it fits patient needs and provides information that is understandable and supports truly voluntary participation.

- The development of patient-friendly protocols, considering factors such as the frequency and duration of visits and the types of invasive procedures that are acceptable to patients.

- The selection of relevant outcome measures, which can fully capture the impact of the condition and are meaningful to patients.

Consulting with relevant patient organizations in the development of informed consent procedures and material, may also be useful. Patient involvement regarding these aspects may contribute to higher recruitment and retention rates and potentially facilitate regulatory approval and funding support.

Useful links:

The European Patients' Academy (EUPATI) recommendations for patient involvement in the informed consent process.

The I-Consent consortium recommendations for designing the informed consent with study participants.

10. Useful resources to develop informed consent templates for MPGN

The European Joint Programme on Rare Diseases (ECRIN) has developed a Rare Diseases Clinical Trials Toolbox to help developers of clinical trials in rare diseases with project design, preparation, and execution. It provides an overview of existing guidelines, recommendations, and templates for informed consent of relevance for rare disease research.

A research group at McGill University in Canada (Nguyen and al, 2019) has developed model consent clauses for rare disease research, that aim to reflect current trends in rare disease research and the needs and wishes of rare disease patients.

The Norwegian Ethics Committees for Clinical Trials on Medicinal Products and Medical Devices (REK KULMU) has developed an informed consent template for studies regulated by the Clinical Trials Regulation.

The Connect4Children website includes an educational resources bank with examples (text, videos) on how to provide information about clinical trials to patients and families.

The coordination and support project "Children Online: Research and Evidence (CO:RE)" has developed examples of tools, including videos, to provide information about participation in research to children and young people and collect their informed consent in an ethical, age-adapted manner.

The I-Consent consortium has developed Guidelines For Tailoring The Informed Consent Process in Clinical Studies to provide information and evidence to assist with the development, or review of the consent process for use in clinical studies with human participants.

The Enpr-EMA's Working Group on Ethics has developed an "Assent / Informed Consent Guidance for Pediatric Clinical Trials with Medicinal Products in Europe", which provides a useful list of assent/consent elements and ideas for how to formulate information points in a way that is understandable and relevant for young people.

11. Glossary of key terms

Key concept	**Definition**
Assent	A minor's affirmative agreement or willingness to participate in a clinical trial. It is a legal requirement in some EU countries for minors of a certain age. *(Clinical Trial Regulation)*
Biomarker	A biological marker is something that can be measured which points to the presence of a disease, a physiological change, response to a treatment, or a psychological condition. For instance, urinary markers such as proteins or enzymes are used as a biomarker in MPGN. *(EUPATI Glossary)*
Biological sample	Blood and urine samples are most used to test for MPGN.
Blinding	Blinding is a method employed to ensure that individuals participating in clinical trial are unaware of their assigned trial arm. In a scenario involving one treatment arm and one placebo arm, for instance, blinding ensures that participants are kept unaware of whether they are receiving the actual treatment or the placebo. Blinding eliminates biases that may arise when participants or the research team know the trial group assignments. In single-blind studies, participants do not want in which are they are, while the research team is informed. In double-blind trials, both participants and the research team are unaware of the assigned arms. *(EUPATI Glossary)*
Clinical trial	A clinical trial is a study where participants are assigned to a predefined therapeutic plan to receive a health intervention, like a medicine, for assessing its effects on health outcomes compared to another treatment or none. Clinical trials are often characterised in Phases from I (first-in-human), II (exploratory), III (confirmatory) to IV (post approval). *(EUPATI Glossary)*
Clinical study arm	Arm refers to each group or subgroup of participants in a clinical trial that receives specific interventions (or no intervention) according to the study protocol. This is usually decided before the trial begins. (Clinicaltrials.gov)

Cluster	A cluster refers to a group of participants (or study sites) that are treated as a single unit for randomization and analysis purposes (ChatGPT)
Complement inhibitor	Complement inhibitors are a class of medications that target the complement system, which is part of the immune system. The complement system plays a role in the body's defense against infections and is involved in inflammation. In certain kidney diseases, an overactive or dysregulated complement system can contribute to damage to the kidney tissue. Complement inhibitors are designed to modulate or block the activity of the complement system to mitigate this harmful effect. (ChatGPT)
Cross-over clinical trial	Trial in which participants receive multiple treatments in a specific sequence. After a defined period, participants switch to a different treatment. This design is often used when comparing two interventions within the same group of participants. (ChatGPT)
Ethics committee / Institutional review board	An independent committee that reviews and approves the protocol for a clinical trial to ensure the protection of participants' rights and well-being. (ChatGPT)
Incidental finding	Incidental findings are previously undiagnosed medical conditions that are discovered unintentionally and during medical evaluation. (Wikipedia)
Inclusion criteria	Inclusion criteria are the characteristics that potential participants must have in order to be considered for participation in a trial (e.g., age, gender, medical diagnosis). They describe the patient population and patient selection criteria. *(EUPATI Glossary)*
Informed consent	A person's voluntary agreement, based on an understanding of the relevant information, to participate in research or a clinical trial, or to undergo a particular medical intervention. *(EUPATI Glossary)*
Patient-reported Outcomes Measures (PROMs)	A patient-reported outcome (PRO) is a measure of the experience or view of a participant in a clinical study. It is not a clinical measure, or an assessment made by anyone else involved in the study. PROs are commonly collected by asking patients to fill in questionnaires, or by interviewing patients. Questionnaires or interview guides used as part of clinical studies should undergo extensive testing to ensure they are reliable and valid. *(EUPATI Glossary)*
Placebo	A placebo is an inactive substance that looks like the drug or treatment being tested. It is used to compare the effects of a new drug in a clinical trial. In many cases, a placebo can be used in addition to standard care, in situations where there is another drug available. (NIH, National Institute on Aging)
Randomized control trial	A randomised clinical trial is one that uses randomisation when allocating people to different arms of the study. For example, in a trial comparing a new medicine with a placebo, each person has an equal chance of being allocated to the medicine or to the placebo group. *(EUPATI Glossary)*
Renal biopsy	A diagnostic procedure involving the removal of a small piece of kidney tissue for examination under a microscope. A renal biopsy is usually performed using a biopsy needle and a local anesthetic. (ChatGPT)

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6. **The IMPACT study - Identifying the perspectives of patients diagnosed with primary membranoproliferative glomerulonephritis and/or parents of patients regarding potential participation in future clinical trials** [http://www.era-decode.eu/downloads/IMPACTstudy_DECODE_Report_Sept2023.pdf]
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