IPOPI
INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

PRIMARY **IMMUNODEFICIENCIES**

# PIDs, **ASSOCIATED CONDITIONS AND CLINICAL TRIALS**

## ABBREVIATIONS

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|---|---|
| IPOPI | International Patient Organisation for Primary Immunodeficiencies |
| PIDs | Primary immunodeficiencies |

PIDs, Associated Conditions and Clinical Trials (1st edition)



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## SUMMARY

Clinical trials are important in advancing medical knowledge and improving patient care and quality of life for people with primary immunodeficiencies (PIDs). These studies can help scientific researchers develop safe, effective treatments and diagnostics, as well as improving understanding of how PIDs develop and progress.

Clinical trials can be observational, investigate new treatments or interventions, or be qualitative and evaluate patients' experiences of living with PIDs. All clinical trials of new treatments go through a series of phases (I–IV) to test whether they are safe and whether they work; each phase must be completed before moving onto the next.

To ensure that any new treatment or diagnostic will work for diverse groups of people with PIDs, scientific researchers must ensure that participants included in clinical trials have distinctive characteristics (e.g. age, gender, ethnicity and disease stage). For each study, people with PIDs must meet the eligibility criteria set out in the clinical trial protocol (study plan).

Even if proposed by a physician, deciding to take part in a clinical trial is something only the individual with a PID can do once they have read the trial protocol. Clinical trials can offer people with PIDs access to treatments that are not yet available clinically; however, there is always a chance that a new treatment will not work or that study participants experience side-effects that require medical attention. It is important, at the outset, to discuss the possible benefits and risks associated with taking part in a clinical trial with the person running the clinical trial (the study investigator) and the healthcare team following the patient throughout the trial.


# INTRODUCTION TO CLINICAL TRIALS

**This booklet explains the types of clinical trials for PIDs, how individuals are selected for clinical trials, what to expect following agreement to take part, and benefits and risks associated with participating in a clinical trial.**

PIDs refers to a large and diverse group of immune disorders caused by defects in the immune system's development and/or function. People with PIDs are immunodeficient and therefore more susceptible to infection and this can have a profound impact on their lives and the lives of their families.[1] While there have been advances in the treatment and management of PIDs in recent decades, there remains an urgent need for new diagnostics and therapies for these conditions as well as a greater understanding of the mechanisms underlying the onset or evolution of certain symptoms.

Human testing of any new treatment or diagnostic for the management PIDs is important and necessary to establish whether it is safe and effective before it is used in the clinic. A new treatment or intervention could include a drug, a medical device, or a biologic (made from living organisms or containing components of living organisms), such as a vaccine, monoclonal antibody, chimeric antigen receptor T-cell (CAR-T) therapy, blood product or gene therapy. Before progressing with clinical trials in humans, laboratory studies are conducted to determine whether the treatment or diagnostic is appropriate and safe enough to evaluate in humans. Results from these studies must be positive and promising before scientific researchers can move on to human testing.[2]

Clinical trials follow a protocol, a carefully designed study plan to safeguard the health of participants and answer specific research questions. Many hospitals, universities, pharmaceutical companies and some charities are involved in clinical trials for new treatments and diagnostics for PIDs and the clinical trials process involves careful consultation and collaboration between healthcare professionals, scientists, research nurses and patients.

# TYPES OF CLINICAL TRIALS AND TRIAL PHASES

There are several types of clinical trials for individuals with PIDs which are summarised in **Table 1.**[3]

**TABLE 1**. Types of clinical trials or research studies for PIDs[3]

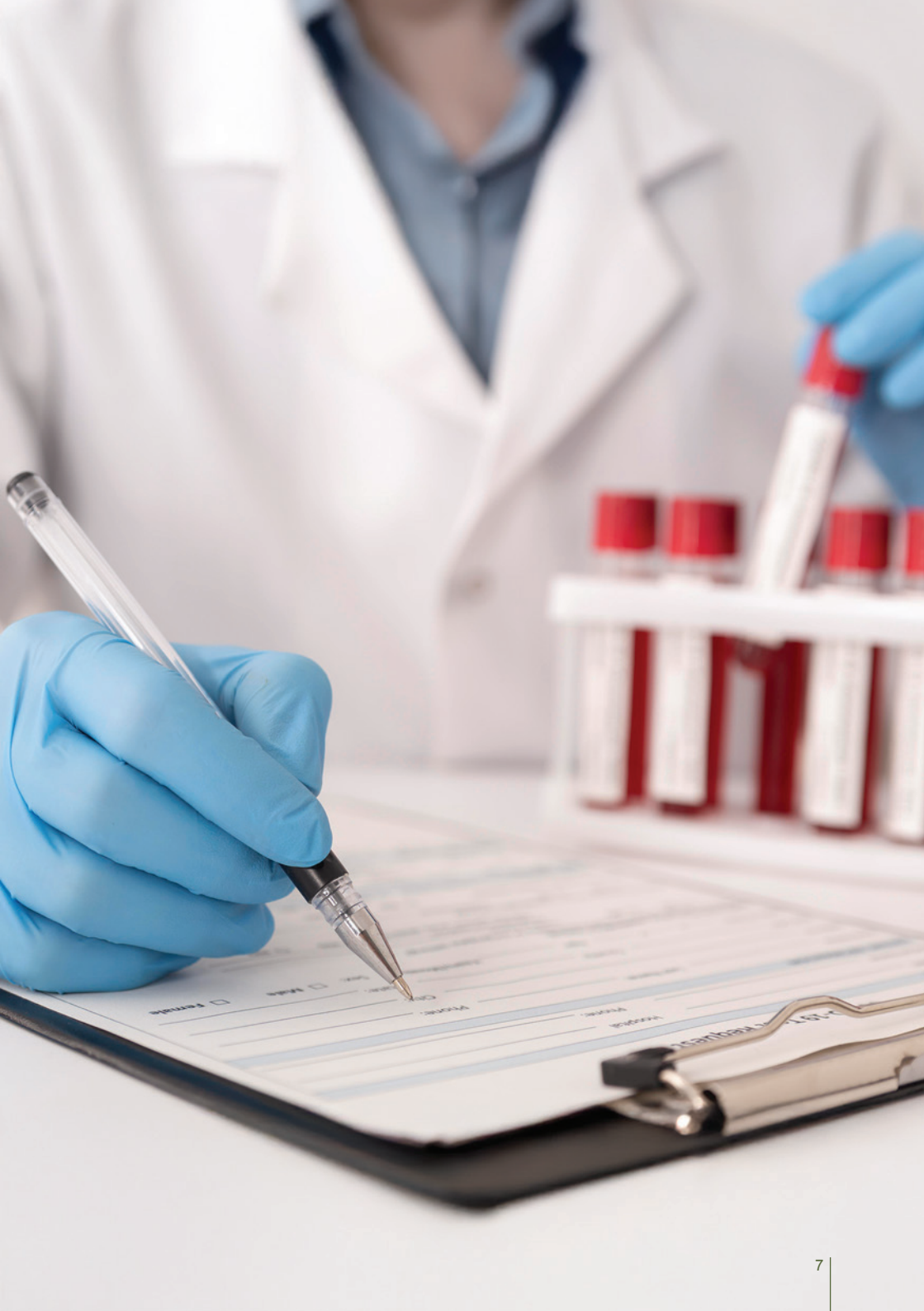
| | What does this type of study involve? | ASSESSMENTS |
|---|---|---|
| **Observational** | An observational study helps researchers understand a PID better or observe trends in a group of people with the same condition. It will not directly affect the participants' health, as no new treatments may be given. | Samples might be taken during the study, e.g. blood samples, lung fluids, sputum.<br>Researchers might ask participants questions using a questionnaire. |
| **Treatment or interventional** | Involves investigation of a new treatment or intervention such as medications (including vaccines), physiotherapy, new devices or innovative approaches to surgery, or radiation therapy. | Researchers will assess how effective and safe the new intervention is.<br>Measures will be dependent on the type of intervention being investigated. |
| **Qualitative** | Qualitative research aims to understand more about people's experience of living with a condition. These studies look at the evolution of a PID (often present since birth) over the lifetime of an individual, to observe any complications or changes in the disorder and learn how to manage these. | Infections with an unusual course Researchers might ask about participants' experiences of anxiety, pain, doing day-to-day activities, to identify patterns that will help them understand the issues faced by people living with a PID, and ways to improve these issues. |

Development of new treatments and diagnostics for PIDs can take many years. For some medications the development process can take 12–15 years before regulatory approval.[4] During this prolonged process, some medications will drop out of development because they are considered unsafe or ineffective. An additional challenge for rare diseases, such as PIDs, includes the low number of patients with the specific PID, making recruitment of a sufficient number of patients difficult.

All clinical trials of new medications go through a series of phases to assess whether they are safe and whether they work. The medicines will usually be assessed against another treatment called a control. This will either be a dummy treatment, also known as a placebo, or an active control/standard treatment already available and approved for use in the condition. Each phase of the process must be safely completed before moving on to the next. These phases of development are summarised in **Figure 1**.[2]

| | | |
|---|---|---|
| **PHASE I** | **Phase I Clinical trials** test a drug or a treatment in a small group of people usually the first time in humans These studies may be done in a group of healthy individuals depending on the treatment or medical condition being studied<br>**Prupose:** To determine if the dose of the drug or treatment is effective and investigate possible side effects | **<100** people |
| **PHASE II** | **Phase II clinical trials** test a drug or a treatment in a larger group of people affected by the medical condition being studied<br>**Purpose:** To investigate initial efficacy and determine the dose(s) that are safe and effective | **100 to 300** people |
| **PHASE III** | **Phase III clinical trials** test a drug or a treatment in a much larger group of people affected by the medical condition being studied. These studies often compare the new drug or treatment with a currently used treatment to compare safety and effectiveness and are the final step bedore regulatory approval<br>**Purpose:** To prove effectiveness and monitor side effects | **300 to ≥ 3,000** people |
| **PHASE IV** | **Phase IV clinical trials** test a drug or a treatment which has already been approved by the regulators and is being prescribed<br>**Purpose:** To determine long-term safety and effectiveness | **300 to ≥ 3,000** people |

**FIGURE 1**. Overview of clinical trial phases[2]



# HOW ARE PATIENTS SELECTED FOR CLINICAL TRIALS?

Many different types of people take part in clinical trials. Some are healthy, while others may have illnesses and are known as patient volunteers.[5] Individuals with PIDs taking part in a clinical trial would be considered patient volunteers.

To ensure that any new treatment or intervention being tested will work for different groups of people with PIDs, it is important that scientific researchers include participants in the clinical trials with different characteristics and from different disease groups.[5] This is the best way to test potential treatments to see whether they should be approved for a larger group. That said, for a treatment that only focuses on one cause of a PID it is critical that only patients affected by the PID are included.

## ELIGIBILITY CRITERIA

To be included in the study, scientific researchers need to ensure that participants meet certain required criteria, which can be with respect to diagnosis, length of diagnosis, age, gender, ethnicity, symptoms and use of background medication. Participants may be excluded from clinical trials because of other underlying health conditions, because they are taking medication that could impact the results of the study or if they have undergone surgical procedures or interventions which could impact the studies outcome.[5] The clinical trial protocol eligibility criteria are not used to reject people personally. Instead, these criteria are used to identify appropriate participants, keep them safe, and help ensure that researchers can find the new information they need.

Often for safety reasons clinical studies of new treatments or interventions are studied in adults before being evaluated in children,[5] unless the condition is one that mostly affects children. Few clinical trials include pregnant women.

# WHAT TO EXPECT IF YOU PARTICIPATE IN A CLINICAL TRIAL

## BEFORE THE TRIAL

It is important for individuals with PIDs planning to take part in a clinical trial to become familiar with the trial protocol before they participate. The trial protocol will generally summarise:[6]

- The goals of the study and research questions
- Who can participate in the study – eligibility criteria
- The schedule and details for treatment

- The visits participants must attend and the location, i.e. hospital or clinic for these visits
- Any procedures, tests or assessments that will be conducted during study visits
- How long the study is expected to last
- The expectations of the study investigator and research team
- Logistical and any financial compensation that accompany the constraints linked to the study (such as travel, hospital visits etc)
- The right to withdraw from the study
- Details about protection and safety of participants.

If the participant agrees with the protocol, they then provide their consent to take part in the study.

## DURING THE TRIAL

Clinical trial participants should expect to be assigned to a particular study group; this generally involves a process of randomisation and may include what is known as blinding.[6] Participants will then undergo a series of tests and assessments at each study visit as outlined in the clinical trial protocol.

### Randomisation

Randomisation is a process used in some trials to avoid bias towards one treatment versus another. One group receives the actual study treatment, while the other will receive the most widely accepted treatment (standard approved treatment).[6] Comparing the results from these two groups often shows which treatment is more effective and/or has fewer side effects. Before participating, it is important for patients to understand that the chance of being randomised into either group is about equal. The study investigator does not decide on what treatment is given, this is usually done randomly by a study statistician or pharmacist.

### Blinding

Blinding is included in clinical trials to prevent bias and to help ensure that the members of the research team and study participants do not inadvertently influence the results of the study. Blinding enables the collection of accurate scientific data. In a "*single-blinded study*", the participants do not know what treatment they are receiving but the research team is aware. For a "*double-blinded study*" neither the research team nor the study participants know what treatment they are receivng.[6]

However, for rare and ultra-rare diseases, such as many PIDs, the low number of available patients makes recruitment and subsequent randomisation of patients within the study a challenge and can result in treatment being non-randomised and non-blind (often referred to as open-label).

### AFTER THE TRIAL IS COMPLETED

After a clinical trial is completed, the research team carefully examine the data collected during the study before making decisions about the meaning of the findings and about the need for further testing.[2] After a phase I or II trial, the researchers decide whether to move on to the next phase or to stop testing the treatment or intervention because it was unsafe or not effective. When a phase III trial is completed, the research team examines the information and decides whether the results have medical importance, and if they can proceed to regulatory approval.

Results from clinical trials can then be published in peer-reviewed scientific journals. If the results are particularly important, they may be featured in the news, and discussed at scientific meetings and by patient advocacy groups before or after they are published in a scientific journal.[2]

## PATIENT SAFETY AND ETHICS

### INFORMED CONSENT

Participants in clinical trials have rights, the most important of which is the right to withdraw their consent from participating in the study at any time without it affecting their care. Informed consent is the process of providing participants information about a clinical study before they accept an offer to take part. Before taking part in a clinical trial, patients will need to sign an informed consent form. This is a document that describes, in detail, the objectives of the clinical trial, what is expected of participants, the potential risks, benefits and any financial compensation offered.[6]

Informed consent is an ongoing process, and participants should be informed about any changes in the study or new findings that may affect willingness to participate.[6]

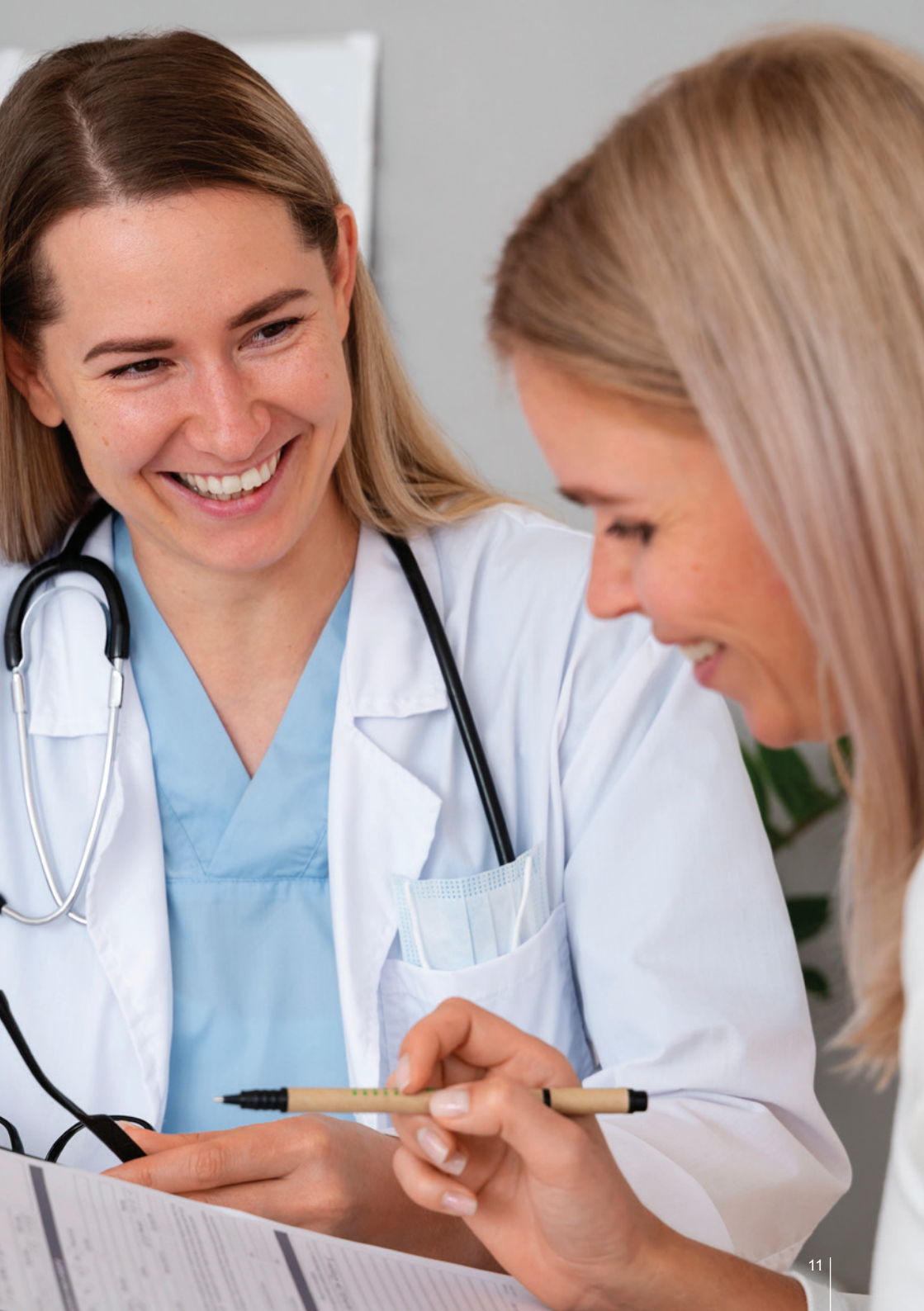
### DATA PROTECTION

Clinical trial participants have the right to privacy; research staff will not be able to share participants' health information with anyone without their consent.

### INDEPENDENT SCIENTIFIC REVIEW

Most clinical trials are reviewed by an independent scientific panel to make sure that they are well designed and meet quality standards. Once this scientific review has taken place, the research team need to fund the study. During this process, another independent review is conducted by the organisation considering funding the study. Only the highest quality research studies are funded.[7]

To assure patient safety and ethical practices, all clinical research is reviewed by an institutional ethics or review board. This panel reviews the proposed study to make sure it is ethical, that the risks do not outweigh the possible benefits and that concerns related to special populations, such as children or pregnant women, if appropriate, are addressed.[7]



### CLINICAL TRIAL SPONSORS

Clinical trial sponsors may be people, institutions, companies, government agencies or other organisations that are responsible for initiating, managing or financing the clinical trial, but they do not conduct the research.[6]

## BENEFITS AND RISKS OF PARTICIPATING IN A CLINICAL TRIAL

Deciding to take part in clinical trials is something only the individual can do once they have all the relevant information about the study from their healthcare team and the study investigator. There are benefits as well as risks and these should be discussed fully before choosing to take part.

### POTENTIAL BENEFITS

Participation in clinical trials may allow people with PIDs to benefit from a treatment option that is not otherwise available. It also enables these individuals to have an active role in decisions that affects their lives and the lives of their families and caregivers. Other benefits of clinical trial participation include more frequent monitoring, opportunities for healthcare professionals to better tailor treatment to individuals by understanding the specifics of their condition and opportunities to meet and interact with people with the same condition.[6,7]

### POTENTIAL RISKS

There is always a chance that the intervention will not work or that study participants experience complications that require medical attention. Known side effects will be described in the Informed Consent Document for the study; however, it is important to consider that there may be other side effects that are not known by the study team at the time of enrolment. A member of the research team will explain and answer any questions about the study, and it is important to consider the risks outlined prior to agreeing to take part.

## FINDING AND CHOOSING A CLINICAL TRIAL

Healthcare teams often ask people with PIDs about taking part in clinical trials or they may want to search for studies themselves. There are many ways to find out more about ongoing studies and which ones would be most suitable and these include clinical trials registries, medical centre websites listing planned or active trials specific to that centre, and patient advocacy group websites. Key clinical trials registries are summarised in **Table 2**.

Participating in clinical trial will usually involve travelling to the place where the research is being conducted, such as a hospital or clinic, and participants should consider logistics before agreeing to participate.2 Although, participants who take part in research will often have their travel expenses paid, logistics should be considered prior to agreeing to participate.

**TABLE 2**. Summary of key clinical trials registries

| | Summary of sources | USEFUL LINKS |
|---|---|---|
| **ClinicalTrials.gov** | A searchable registry that provides information about a trial's purpose, who may participate, locations and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. | https://clinicaltrials.gov/ |
| **National Institute of Health (NIH)** *USA only* | The NIH maintains an online database of clinical research studies taking place at its Clinical Centre, which is located on the NIH campus in Bethesda, Maryland, USA. | https://clinicalstudies.info.nih.gov/ |
| **ResearchMatch** *USA only* | ResearchMatch is a nonprofit program funded by the NIH. It helps to connect people interested in research studies with researchers from top medical centres across the USA. | https://www.researchmatch.org/ |
| **European Union (EU) clinical trials register** | The European Union Clinical Trials Register allows people to search for protocol and results information on:<br>Interventional clinical trials that were approved in the EU/European Economic Area (EEA) under the Clinical Trials Directive 2001/20/EC.<br>Clinical trials conducted outside the EU/EEA that are linked to European paediatric-medicine development. | https://www.clinicaltrialsregister.eu/ctr-search/trial/2009-011434-10/3rd |
| **Pan African Clinical Trials Registry** | The Pan African Clinical Trials Registry (PACTR) is a regional register of clinical trials conducted in Africa.<br>PACTR provides a searchable, electronic database of planned trials and trials currently in progress. | https://pactr.samrc.ac.za/ |

It is natural for families and caregivers to have concerns about participation in clinical trials and people with PIDs should try to address these wherever possible. It is important to provide caregivers and families with as much information as possible about the trial to reassure them that the decision is well-considered, and that safety is a top priority in the trial.

## QUESTIONS TO ASK BEFORE PARTICIPATING IN A CLINICAL TRIAL

If you are thinking about taking part in a clinical trial, it is important to ask your healthcare team any questions or bring up any issues concerning the trial at any time. Potential questions that could be important to ask are summarised in **Table 3**.[6,7]

**TABLE 3**. Questions prospective clinical trial participants may ask their healthcare team[6,7]

| | Questions |
|---|---|
| **The trial** | • What is the purpose and goals of the clinical trial?<br>• What PID is the new treatment or intervention aimed at?<br>• Why does the research team think that the new treatment or intervention may be effective for my PID?<br>• Who is the clinical trial sponsor?<br>• How are trials results and safety of participants being monitored?<br>• How long will the trial last?<br>• What will my responsibilities be if I take part?<br>• Will I be informed about the results of the trial? |
| **Benefits and risk** | • What are my possible short-term benefits if I participate?<br>• What are my possible long-term benefits if I participate?<br>• What are my short-term risks, and side effects?<br>• What are my long-term risks?<br>• What other options are available, and are there other trials which might suit me better?<br>• How do the risks and benefits of this trial compare with those options? |

| | Questions |
|---|---|
| **Participation and care** | • What kinds of treatment, procedures and/or tests will I have during the trial?<br>• Will they hurt or cause discomfort and, if so, for how long?<br>• How do the assessments in the study compare to those I would have outside of the trial?<br>• Will I be able to take my regular medications (e.g. IgG replacement therapy, antimicrobial prophylaxis) while taking part in the clinical trial?<br>• Where will I have my medical care (hospital/clinic)?<br>• Who will oversee my care?<br>• What will happen after the trial if the new treatment is much better than my usual treatment? Will I be able to continue with it? |
| **Personal issues** | • How could being in this study affect my daily life?<br>• Can I talk to other people who are taking part in the study?<br>• What infection control protocols will be in place during trial visits? |
| **Financial considerations** | • Who will fund the clinical trial?<br>• Will I have to pay for any part of the trial such as tests or the study drug? If so, what will the charges be?<br>• What is my health insurance likely to cover? (If applicable)<br>• Who can help answer any questions from my insurance company or health plan? (If applicable)<br>• Will there be any travel or childcare costs that I need to consider while I am in the trial? |

## OTHER RESOURCES

In addition to using the key clinical trials registries summarised in Table 2 to find on-going clinical trials, IPOPI has the PID Life Index (https://pidlifeindex.ipopi.org/#/en/principles/world-map), which is an interactive tool built on 6 key principles of care that measures the status of the PID healthcare environment in a country. The PID Life Index ranks countries from 0% (lowest) to 100% (highest) on the basis of the 6 Principles of Care: PID diagnosis, National Patient Organisations, Registries, Specialised centres, Treatments, and Universal health coverage.

# FURTHER INFORMATION AND SUPPORT

This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI). Other booklets are available in this series. For further information and details of PID patient organisations worldwide, please visit **IPOPI.org**.

Provided by

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Supporting families affected by primary and secondary immunodeficiency

## REFERENCES


[1] Meyts I, Bousfiha A, Duff C, et al. Primary immunodeficiencies: A decade of progress and a promising future. Front Immunol 2021; 11: 625753.

[2] National Heart Lung and Blood Institute (NHLBI). Clinical trials: How clinical trials work. https://www.nhlbi.nih.gov/research/clinical-trials/how-studies-work (Accessed August 2024).

[3] Kandi V, Vadakedath S. Clinical trials and clinical research: A comprehensive review. Cureus 2023; 15: e35077.

[4] Hughes JP, Rees S, Kalindjian SB, et al. Principles of early drug discovery. Br J Pharmacol 2011; 162: 1239-1249

[5] National Heart Lung and Blood Institute (NHLBI). Clinical trials: Who can participate. https://www.nhlbi.nih.gov/research/clinical-trials/participating (Accessed August 2024).

[6] National Institute of Health (NIH). Clinical trials and you: The Basics. https://www.nih.gov/health-information/nih-clinical-research-trials-you/basics (Accessed August 2024).

[7] National Heart Lung and Blood Institute (NHLBI). Clinical trials: Benefits, risks, and safety measures. https://www.nhlbi.nih.gov/research/clinical-trials/safety-benefits-risks (Accessed August 2024).


'Information presented within this leaflet is based on published literature at the time of production. The leaflet is intended to provide a broad overview rather than be a guide on clinical practice – for this, please consult the treatment guidelines in your country.'

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