UNIVERSIDADE D
COIMBRA

Diogo Alexandre Carvalho Pedroso

ETHICAL CONSTRAINTS IN PSYCHIATRIC CLINICAL RESEARCH

Dissertação no âmbito do Mestrado em Patologia Experimental orientada pelo Professor Doutor Carlos Alberto Fontes Ribeiro e apresentada à Faculdade de Medicina da Universidade de Coimbra.

Julho de 2019

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“Success consists of going from failure to failure without loss of enthusiasm.”

Winston Churchill

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Conflicts of Interest Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this master thesis.

Abstract

Psychiatric disorders are prevalent and/or incident pathologies that deeply affect one's mind and can present high rates of comorbidities as result of the pathologic phenomena. The individuals affected are more vulnerable to ethical constraints not only in a social context but also regarding the clinical practice as well as research. This review proposed to analyse and discuss the most relevant and recent literature regarding the ethics towards the design and conduction of clinical studies. The research question – Which ethical constraints affect patients with psychiatric disorders in a clinical research context (compared to standard patient care / non-psychiatric patients)? – was developed in accordance with the defined "PICO strategy" and the literature assessment was done respecting the defined eligibility criteria. The search strategy assessed a total of one thousand and nine [1509] publications – PubMed, PsycINFO and UpToDate– using the Mesh Terms: "psychiatry" , "mental disorders" , "clinical research" and "ethics", and resulted in a total of thirty-six articles included – twenty-five review articles, five original articles, three clinical case study and three opinion articles. The most relevant topics – research & scientific value; participant selection and recruitment; financial incentives; risk-benefit ratio assessment; informed consent; particular aspects of the clinical trials; special contemporary issues; other issues – were assessed and discussed through an ethical perspective and solutions have been proposed when possible. This review concludes that the ethical principles and values applied towards psychiatric clinical research constitutes one of the major phenomena to ensure the scientific and social validity of clinical studies regarding all its domains (design, conduction and publication).

Keywords: "Psychiatry"; "Mental disorders"; Clinical research; Ethics; "Cognitive Impairments"; "Decision-making capacity"

Resumo

Os distúrbios psiquiátricos são patologias prevalentes e/ou incidentes que afetam profundamente a mente podendo resultar em rácios elevados de comorbilidades derivadas dos mecanismos patológicos inerentes a estas patologias. Os indivíduos afetados são mais vulneráveis a constrangimentos éticos, não apenas em contexto social, mas também num contexto de prática clínica como em investigação. Esta revisão propôs-se a rever a literatura mais relevante e recente acerca da ética aplicada ao desenho e condução de estudos clínicos. A questão de investigação definida – "Quais os constrangimentos éticos que afetam doentes com distúrbios psiquiátricos no contexto de investigação clínica (comparativamente aos cuidados médicos standard / doentes não psiquiátricos?" – foi desenvolvida de acordo com a estratégia de PICO definida. A avaliação literária foi realizada de acordo com os critérios de elegibilidade definidos. A estratégia de revisão da literatura avaliou um total de mil quinhentos e nove [1509] publicações – PubMed, PsycINFO e UpToDate – utilizando os termos Mesh: "psychiatry", "mental disorders", "clinical research" e "ethics"; resultando num total de trinta e seis artigos incluídas – vinte e cinco artigos de revisão, cinco artigos originais, três casos clínicos e três artigos de opinião. Os tópicos mais relevantes – valor da investigação & científico; seleção e recrutamento de participantes; incentivos financeiros; avaliação do rácio risco-benefício; consentimentos informados; problemas particulares dos ensaios clínicos; outros problemas – foram avaliados e discutidos através de uma perspetiva ética e soluções foram apontadas sempre que possível. Esta revisão conclui que os princípios e valores éticos aplicados em direção à investigação clínica psiquiátrica constituem um dos principais fenómenos para assegurar a validade científica e social dos estudos clínicos em todos os seus domínios (desenho, condução e publicação).

Palavras-chave: "Psiquiatria"; "Distúrbios psiquiátricos"; "Investigação clínica"; "Ética", "Défices cognitivos"; "Capacidade de decisão"

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Abbreviation List

C

CI – Cognitive Impairment

D

DMC – Decision-making Capacity

E

ED – Experimental Drug

N

NC – Nuremberg Code

P

PI – Principal Investigator

R

RCT – Randomized Clinical Trial

Chapter I

Introduction

I. Introduction

1. Background

Health care is one of the main standards of any modern society in order to preserve or augment the life quality of its citizens. It is defined by the Merriam-Webster dictionary as the “efforts made to maintain or restore physical, mental, or emotional well-being especially by trained and licensed professionals”. (1)

On the other hand, a society is “a community, nation, or broad grouping of people having common traditions, institutions, and collective activities and interests”. (2) It can be classified as a changeable environment, similar to the medical conditions and needs that affect the people inserted in such society. This translates in an adaptable health care format and provision according to the society in which it is inserted and the needs of the individuals themselves. Such paradigm is only valid in a constant state of changing and improvement, made not only by the significant positive change in the provision and access to medical care but also by the progress of scientific and medical research in order to improve the health condition of that population in a broad spectrum. Scientific and medical research is one of the fundamental pillars of modern medicine constituting the means by which clinical knowledge is obtained. Behind every element used to prevent, diagnose or treat a medical condition lay several years of careful investigation.

Ethics is defined as “the principles of conduct governing an individual or a group” (3) representing the main philosophic principles by which a society is governed. The ethical principles and values have been a study subject starting centuries ago, originating debates concerning different approaches or interpretations of its principles. Health care and all its constituting domains, given an example in the research context, as inserted in society are affected by the philosophic principles of the society in which is conducted. As such, the research designed and conducted in those parameters is deeply influenced by those philosophies.

In the clinical research domain, as in medical care, the ethical principles govern not only what should be done but also how it should be done. Given an example, in order to conduct a clinical study protocol, its design must be ethical and predict far superior benefits compared to the potential maleficence.

2. Work relevance

In the scientific milieu, ethics and research are two major topics of discussion with hundreds of articles, and other forms of scientific publications, published every year. The assessment of those scientific publications drives towards an intrinsic relation between the ethical principles and the design and conduction of clinical studies. In other words, the ethical principles applied to clinical research constitute a hot topic in modern medicine. The ethical principles immutably influence clinical research, being those principles asserted as the moral standard for its design and conduction.

The advances in scientific knowledge coupled with the social evolution of moral principles created a focus in previously disregarded or outcasted niches and the psychiatric disorders are a perfectly illustrative example of such statement. In modern times it is often discussed through dozens of publications found directed towards the intrinsic ability of the ethical principles and psychiatric clinical research, in such way that can now be asserted as a “hot” topic in modern medical ethics. Although such evolution is unquestionable, much work is still left undone concerning ethical issues that persist as ethical paradigms and the contemporary ones created by the progression of science and technology.

This review is framed in the discussion of the ethical paradigms in clinical research of psychiatric disorders. The authors proposed to analyse and discuss the most relevant and recent publications in order to clarify and originate new and more informed debate in hopes to one day the resolution of such ethical dilemmas in psychiatric clinical research may be achieved.

3. Objectives

The main objective of this master thesis is to analyse and summarize, through a deep systematic review of the contemporary literature, the ethical constraints in psychiatric clinical research.

The subsequent objectives originated as a consequence of the main objective, are to critically analyse and systematize the literature focused on the ethical issues transcending to all fields of clinical research and those that are directed to the psychiatric population, while resorting to clinical cases as examples, pointing possible solutions and originate an informed and reasoned debate.

The objectives described are in accordance with the established “PICO strategy” and the resultant research question – Which ethical constraints affect patients with psychiatric disorders in a clinical research context (compared to standard patient care / non-psychiatric patients)? – as defined in Chapter II “Methods”.

Chapter II

Theoretical Fundaments

II. Theoretical Fundaments

1. Psychiatric Disorders

A psychiatric disorder is a syndrome defined by clinically significant prejudice in the cognitive, emotional and behavioural domains reflecting in a dysfunction in the individual´s psychologic and biological functions. A mild to severe impairment is expected to affect social, professional and other important and/or daily activities. It is of most importance to clearly define what is a psychiatric disorder and what is a deviation of social “adequate” behaviour. A social deviation may be the result of a traumatic event (e.g. death of a close familiar/friend) or an “out of the norm” culture (e.g. emigration from an undeveloped country to the United States of America) while a psychiatric disorder is a result of a subjacent individual dysfunction. (4)

The pathological disorders that characterize the field of psychiatry are studied according to the two fields of psychopathology, descriptive and experimental. Descriptive psychopathology, also known as phenomenological, focus in an objective clinical view of the disorders, excluding previously formed concepts or theories, in order to perceive, in the most accurate way possible, the conscious and observable behavioural phenomena. Its main goal is to understand the individual morbid mental experiences/illness. Experimental psychopathology, by contrast, aims to explain and describe subjacent pathological mechanisms of the conscious and unconscious morbid mental experiences using experimental methods, such as functional brain imaging. Therefore, its main goal can be described as the search for the pathological mechanisms that are underneath the shown symptoms. (5)

The psychiatric disorders (see Table II.1.) can be categorized into three main branches: mental health and behavioural disorders, substance-use disorders and neurological disorders (neuropsychiatric or organic psychiatric disorders). Mental health disorders are determined in the behavioural domain by the abilities to manage and deal with emotions, behaviours and the necessity for human interaction, but also by determinants of the social-economic domain (e.g. environmental factors). Other factors influence mental health such as genetic predisposition, environmental stress or hazards and infections in newborns. Some of the most eminent mental disorders are schizophrenia, depression and bipolar disorders, which present a high prevalence and comorbidity worldwide. (6)

Schizophrenia is a high comorbidity associated disorder with an estimated prevalence of 0.25 to 0.64 per cent all around the globe. (7) It is characterized by psychotic experiences including delusions and hallucinations, creating high cognitive and social-economic impairments.

Depression is possibly the most common mental disorder and one of the major causes of cognitive and social-economic disabilities, affecting an estimated number of three in one hundred individuals. The assessed prevalence shows an unequal distribution according to the sex of the individual, affecting a larger number of females in deterioration of male individuals. Bipolar disorder is a pathology of the psychiatric forum portrayed by variable episodes of mania – exacerbated emotions and self-esteem, and a diminish need of sleep – and depression, interceded by normal mood periods. In modern medicine, the use of mood stabilizers shows high evidence of effectiveness in the treatment of the acute phase of bipolar disorder and the prevention of relapses. (6)

The World Health Organization developed and implemented an Action Plan starting in the year two thousand and thirteen (2013), and with a planned ending date of two thousand and twenty (2020), in an attempt to promote and improve mental and social health care for psychiatric patients all around the world. (6)

Table II.1. Major Psychiatric Disorders according to DSMV (4)

Major Psychiatric Disorders
Neurodevelopment Disorders
Schizophrenia Spectrum and Other Psychotic Disorders
Bipolar Disorder
Depressive Disorders
Anxiety Disorders
Obsessive-compulsive Disorders
Trauma and Stress-Related Disorders
Dissociative Disorders
Somatic Symptoms and Related Disorders
Feeding and Eating Disorders
Elimination Disorders
Sleep-wake Disorders
Sexual Dysfunctions
Gender Dysphoria
Disruptive, Impulse-control, and Conduct Disorders
Substance-related and Addictive Disorders
Neurocognitive Disorders
Personality Disorders
Paraphilic Disorders

i) Social-economic Inequalities

Inequality is defined by the Merriam-Webster dictionary as “the quality of being unequal or uneven” in several domains such as “social disparity” and “disparity of distribution or opportunity”. (8) Although societies tend towards the extinguishment of any disparities, particularly social and economic inequalities, they are still highly prevalent. The origins of such disparities can come by means of race, sexuality, social status, education and others.

Evidence shows a negative association between social status and the prevalence of psychiatric disorders. Several studies published have analysed socio-economic factors, such as education, unemployment and low incomes, demonstrated a negative influence on the life quality of the population and have shown its effects as a substantial disadvantage when compared to higher socio-economic backgrounds. Individuals with a lower socioeconomic status, as consequence to their disadvantage panorama, when compared to higher socioeconomic status individuals, tend to demonstrate a higher prevalence of mental health disorders. (9)

The persistent stigma and discrimination can also be a highly influencing factor in creating or aggravating the inequalities experienced by psychiatric patients, resulting in unequal access to health (or social) services. In the specific case of disorders characterized by psychoses or similar, there is an increased risk of human rights violations such as prolonged forced confinement in institutions. (6)

ii) Treatment in Psychiatric Disorders

The provision of treatment for psychiatric disorders shows an evident gap between the treatment needed and the treatment received. In developed and rich countries, a range between thirty-five and eighty-five per cent lack adequate treatment while those numbers appear to be between seventy-six to eighty-five per cent in underdeveloped and poor countries. The quality of the received treatment also constitutes a determinant of outcome for psychiatric pathologies. (6)

Treatment for psychiatric disorders (see Table II.2.) are typically associated with seven pharmacologic drug groups depending on the intended outcome(s), consisting of **anxiolytic** – treatment of anxiety symptoms –, **hypnotics** – sleep improvement –, **antipsychotics** – psychosis symptom control –, **anticholinergics** – treatment of extrapyramidal side effects –, **antidepressants** – improvement of depressive symptoms –, **mood-stabilizers** – stabilization of mood swings – and **psychostimulants** – increase of the activity of the central nervous system through sympathomimetic effects.

Table II.2. Common Psychiatric Medication & Respective Outcomes

Drug type	Intended Outcome
Anxiolytic drugs	Anxiety symptoms control
Hypnotics	Sleep improvement
Antipsychotic drugs	Reduction of psychomotor excitement
	Control of psychotic symptoms
Anticholinergic drugs	Control of extrapyramidal side effects
Antidepressant drugs	Improvement of depressive symptoms
Mood-stabilizing agents	Improvement of mood swings
Psychostimulants	Increase the activity of the central nervous system

2. Schizophrenia

Schizophrenia is a psychiatric disorder with a multifactorial aetiology mostly attributed to altered biochemical phenomena [dopamine, glutamate, serotonin (5-HT) and inflammatory markers], cumulative genetic mutations, history of alcohol and drug abuse, and the environment in which the patient is inserted (psychological factors). Several studies point to a hereditary susceptibility to developing schizophrenia, in which the cumulative effect of several susceptibility genes (e.g. polymorphisms) may originate the development of the disease. Substance and alcohol abuse represent an augmentation of the risk to develop a psychiatric disorder, being the risk of schizophrenia cases in those populations over twice as high. Other factors are described in the literature, such as functional/organic disorders (e.g. decrease of frontal lobes) and microstructural dysfunctions (e.g. dopamine levels), but these present a lack of overall consent or indisputable evidence. From a conceptual point of view, it is very challenging due to the unpredictability of the syndrome itself, but also due to the heterogeneous classification attributed by different countries and different specialists. (10)

i) Clinical Aspects

The **positive symptoms**, also known as productive or “first-rank” symptoms, are commonly described featuring hallucinations and deliriums, but possible of being accompanied by others such as alterations of speech (form, possession, and course), thought, and behaviour. (10)

Hallucinations can be described as experienced perceptions that had no stimulus in the respectively associated organ to fundament it. This clinical manifestation is described according to complexity, sensory modality, and special features. (10) In schizophrenia, auditory hallucinations are the most common type of hallucinations, normally being the voices heard in an imperative or aggressive tone accompanied by a derogative content. (11)

Delusions are very common in schizophrenia and deeply affect the person's vision of the world and/or of himself. They can be defined as a strong erratic belief, immutable by logical arguments or proves to the contrary, and not framed in the patient cultural, religious, and educational setting. The most common delusions in schizophrenia are **persecutory** (e.g. belief of a partner’s intention and/or attempt to murder them), **delusional perception** (abnormal perception of a received stimulus), **passivity** (delusions of reference and control – belief of external agents partial or full control over oneself actions – e.g. patients believe that the electronic waves emitted by his neighbour´s dish antenna are controlling his actions and he cannot resist them), **possession of thought** (thought withdrawal, insertion or thought

broadcasting – belief of his thoughts being robbed/lost or inserted in oneself´s mind, or his own thoughts are being transmitted to others – e.g. patient self-belief that his thoughts are being taken by a third entity and for that reason he cannot organize a rational, continuous and coherent reasoning). (10)

The **negative symptomatology** represents a lower impact on schizophrenic patient's life. Characteristically described as a partial or total loss of the normal psychological functional domains (Table II.3.), this can appear as a core symptom of the schizophrenia deficit or as a secondary outcome if its development is a direct consequence of positives symptoms. (11)

Table II.3. Negative Symptoms & Dysfunctions

Domains	Dysfunction Description
Affective flattening	Reduction of emotional expression (amplitude and intensity)
Social	Decrease of social interaction
	Decrease of affective interactions and commitment
Anhedonia	Partial or total loss of the ability to feel interested or pleasure
Alogia	Reduction in speech spontaneity and content
Avolition	Lack of motivation and initiative

Other symptoms are described beyond the positive or negative symptoms, such as **behavioural disorganization** (formal thought disorder, inappropriate affect or bizarre behaviour), **cognitive symptoms** that can produce attention, learning and memory impairments, and **insight impairment** (e.g. not accepting his own condition but attributing guilt of the disease´s outcomes to external entities). Mood alterations, in association or not with other comorbidities, may be present in schizophrenic patients (e.g. depressive mood, irritability, anxiety or euphoria). (10)

During the **acute phase** of the schizophrenia disorder, there is a predominance of positive symptoms and behavioural disorganization and, by contrast, the negative and cognitive symptoms are less predominant or, at least, less noticeable by the exacerbation of the positive ones. After the successful therapeutic implementation, evidence shows a reminiscence of positive symptoms, starting the **chronic phase** in which, although some positive

symptomatology may persist, negative symptoms are the defining clinical panorama found. The discontinuation of medication and/or a negative response to life events may exacerbate the positive symptoms, returning to an acute phase. Although the highly variable nature of both phases/symptomatology between patients, some factors influence a poor prognosis such as demographic factors, the severity of cognitive impairments, and poor treatment adherence. (10)

ii) Treatment and Management

The treatment and management in schizophrenia (Table II.4.) consist of several domains that must be well articulated and closely monitored in order to archive the best prognosis possible. Strong evidence obtained from several randomized clinical trials and clinical practice shows that the resort to pharmacological treatment, especially antipsychotic drugs, is mandatory to prevent relapses (acute phase/positive symptoms exacerbation). Some limitations in antipsychotic drugs, such as low effectiveness, severe side effects and the exclusive effect on positive symptoms, constitute a decisive factor in the patient´s prognosis and overall quality of life.

The choice of which antipsychotic drug to prescribe comes down to the overall subjective adjustment according to the patient´s different drug profile/tolerance, since the differences between responses to different drugs in the antipsychotic group (typical or atypical) in schizophrenia are not clinically significant being achieved significant therapeutic response in around seventy to seventy-five per cent (70 - 75%) of the treated population. In the treatment for resistant schizophrenia (non-clinically significant response to “traditional” antipsychotics) it often comes to the resource of clozapine. According to consensus and therapeutic guidelines, antipsychotics should be prescribed in the lowest effective dose and adjusted according to the patient’s outcomes. (10)

Non-pharmacologic therapies are recommended alongside with pharmacological treatment in order to achieve the best prognosis possible. It is recommended the establishment of behavioural therapy (e.g. professional accompaniment, familiar interventions).

Table II.4. Typologies of Schizophrenia Treatment

Treatment of schizophrenia			
Treatment typology	**Classes**	**Specifications**	
Pharmacologic	Antipsychotic drugs	Typical	–/–
		Atypical	Clozapine
	Antidepressant drugs	Tricyclic	
		Selective serotonin reuptake inhibitors	
		Noradrenaline reuptake inhibitors	
		Monoamine oxidase inhibitors	
		Others	
	Mood stabilizers	–/–	
	Benzodiazepines	–/–	
	Future drugs	–/–	
Psychological	Family therapy	–/–	
	Cognitive behaviour therapy	–/–	
	Cognitive remediation	–/–	
	Other psychological interventions	Social skills training	
		Art therapies	
		Dynamic psychotherapy	
		Exercise	
		Adherence therapy	
Others	Electroconvulsive therapy	–/–	

3. Depressive Disorders

The term depressive disorder is currently used to refer to the medical conditions in which the main feature is an abnormality of mood, translating in the reason why they are also mentioned as mood or affective disorders. In the past, states of anxiety were also included in this cluster, but this term is nowadays usually restricted to disorders in which depression and elation define the humour. Humour is a generalized and sustained feeling, internally experienced, that influences behaviour and perception of the surrounding world. It can be normal (euthymic), elevated or depressed, with healthy people undergoing a great variety of states. By contrast, carriers of a mood disorder live through a persistently elevated or depressed state which is associated with underlining suffering for the patient and prejudice on interpersonal, social and occupational functioning. (12,13)

There are various types of these disorders: major depression, dysthymia, bipolar disorder and cyclothymia. The first two syndromes, which will be the focus, present only depressive states, being characterized by the central features: depressed mood, anhedonia, depressive cognitions, adynamia and psychomotor retardation.

i) Clinical Aspects

Depressive disorders are frequent psychiatric disorders affecting approximately ten per cent of the world's population, being one of the most common causes of disablement and suicide, therefore the importance of recognizing the various clinical presentations. The patient's appearance is characteristically affected, while not a requirement, and can be perceived by the practician throughout the clinical interview: sad facial and corporal expressions, with bent shoulders and head inclined forward, downward gaze, tendency to cry, neglected attire and grooming. (12,13)

Depressed mood is the most prominent symptom, present in over ninety per cent of patients, with mentions of misery, sadness, feeling hollow and hopelessness. This mood is pervasive, showing no substantial improvement in conditions where there would be easing of ordinary feelings of sadness, with the patient being able to distinguish between this state and the experience of conventional sadness. This mood change can sometimes be concealed making it more difficult for the practician to perceive. Nonetheless, a small portion of patients do not report a depressed mood but rather apathy and lack of sorrow or even irritable mood, especially in infants and adolescents.

Anhedonia, another frequent, whilst not always spontaneously mentioned, symptom adds to the deviation of mood, being the lack of interest and enjoyment towards activities previously pleasant to the patient. It is often reported as feeling lethargic and finding everything an effort, leading to unfinished tasks and a decline in work and academic achievements. Loss of sexual drive and libido may also be present, resulting in distress in intimate relationships or marital conflicts.

Depressive cognitions occur in patients with a depressive disorder often present with negative thoughts, which means there is a distortion of reality turning their thoughts and feelings into negative ones. These can be divided into three groups: worthlessness, pessimism and guilt. The feeling of worthlessness is characterized by a lack of self-confidence and esteem associated with the notion that the people surrounding the patients perceive him as a failure. The pessimistic thoughts refer to prospects meaning patients foresee and expect the worst possible outcomes, which often leads to ideas of hopelessness and loss of meaning for living, contemplating death as a welcome release - this “may progress to thoughts of, and plans for, suicide”. Guilt takes on the form of self-condemnation: the patients self-blame for every sad memory, failure or misfortune encountered, “for their misery and incapacity, and attribute it to personal failing and moral weakness”. (12)

Adynamia is commonly referred to by patients as a lack of energy or tiredness, very frequent in depressive disorders, being either mental, physical or both. This leads to the patients’ tendency to remain in bed and isolated.

Psychomotor retardation affects around half of the patients, who develop slowness, translating into a slowing of thought which reflects in speech and movement impairment (psychomotor retardation). This can be appreciated by a diminishing in content or amount of speech, with an increased latency time before answering questions, lack of spontaneous movements as well as apathy. Nevertheless, a great number of patients may present with agitation, a state of restlessness experienced as an inability to relax which is perceived by an observer as a restless activity.

ii) Treatment and Management

Evidence provided by clinical practice and research shows that a better prognosis of depression is found in individuals that have been submitted to a combination of pharmacological and psychological therapy (Table II.5.). In an **acute onset**, the pharmacologic treatment has the intent to improve symptomology and relays on the use of antidepressant drugs, lithium (as sole or combined therapy with antidepressant drugs), anticonvulsants and

atypical antipsychotic drugs. On another hand, the psychological treatment relays on the application of the following coping techniques: supportive psychotherapy, cognitive behaviour therapy, interpersonal psychotherapy, behavioural activation, marital therapy and dynamic psychotherapy. Other treatments, such as electro compulsive therapy, sleep deprivation and bright light treatment, have shown positive clinical evidence, although their use is conditioned by specific individual clinical cases. (12)

Table II.5. Typologies of Depression Treatment

Acute treatment of depression		
Treatment typology	**Subcategories**	**Specifications**
Pharmacologic	Antidepressant drugs	Tricyclic
		Selective serotonin reuptake inhibitors
		Noradrenaline reuptake inhibitors
		Monoamine oxidase inhibitors
		Others
	Lithium	Sole treatment
		Combination with antidepressants
	Anticonvulsants	–/–
	Atypical antipsychotic drugs	–/–
Psychological	Supportive psychotherapy	–/–
	Cognitive behaviour therapy	–/–
	Interpersonal psychotherapy	–/–
	Behavioural activation	–/–
	Marital therapy	–/–
	Dynamic psychotherapy	–/–
Other	Electroconvulsive therapy	–/–
	Sleep deprivation	–/–
	Bright light treatment	–/–
The chronic treatment of depression		
Pharmacologic	Antidepressant drugs	Same as above
Psychotherapy	Cognitive therapy	–/–
	Interpersonal therapy	–/–

4. Clinical Research

The ultimate intent of clinical research is to archive clinical data that provide evidence regarding a hypothesis, a diagnose/prevention method, or an intervention. Although such aspects may have been tested in non-human models, since the results are objectively towards for human use/benefit, only the use of a human model can provide strong evidence that substantiates the clinical practice. Clinical research is categorized, according to the study type, in observational studies and experimental studies (Figure 1.).

Observational studies do not require direct intervention to the participant, being the clinical data acquired only through the observation and without the Principal Investigator (PI) having any control over the variables.

Cohort studies are applied when the main goal is the identification of future outcomes after exposure to a determinate agent - prospective – or the main goal is the identification of past exposure to an agent that caused a present outcome(s) – retrospective. In the first study, population is chosen according to the exposure to an agent and the second selection it is based on one or more outcomes. (14)

Case-control studies' main goal is the identification of cases that match a determined outcome and measure the influence of the exposure to one or more risk factors that occurred in the past. The study population is selected based on the selected outcome(s). (14)

Cross-sectional studies' main goal is to collect, simultaneously, data of the outcomes and of the exposure to one or more risk factors, being the participants chosen by the inclusion and exclusion criteria previously set. (14)

Experimental studies are used to test an intervention, providing clinical data through measurement of the change of one or more factors previously defined. According to the intervention being studied, the use of a control group may be necessary to archive clinical evidence, meaning the intervention group must be compared to a non-intervention group, in order to assure that no other variables deemed not clinically significative have influenced the outcomes measured. In controlled trials, it is often applied a randomization method that allocates participants to the different study arms (e.g. control arm vs intervention arm) without selection bias, assuring participants have the same statistical probability of being allocated in any of the study's arms.

Each one of these studies applies to a specific situation depending on the main goal of the clinical study. Their relevance in terms of support to the medical decision depends on its applicability to the medical practice. Their categorization occurs in order of impact in the

medical care categorized on a scale from one to five. On the level one the studies type that demonstrate better evidence of applicability and on the level five the exact opposite. (14)

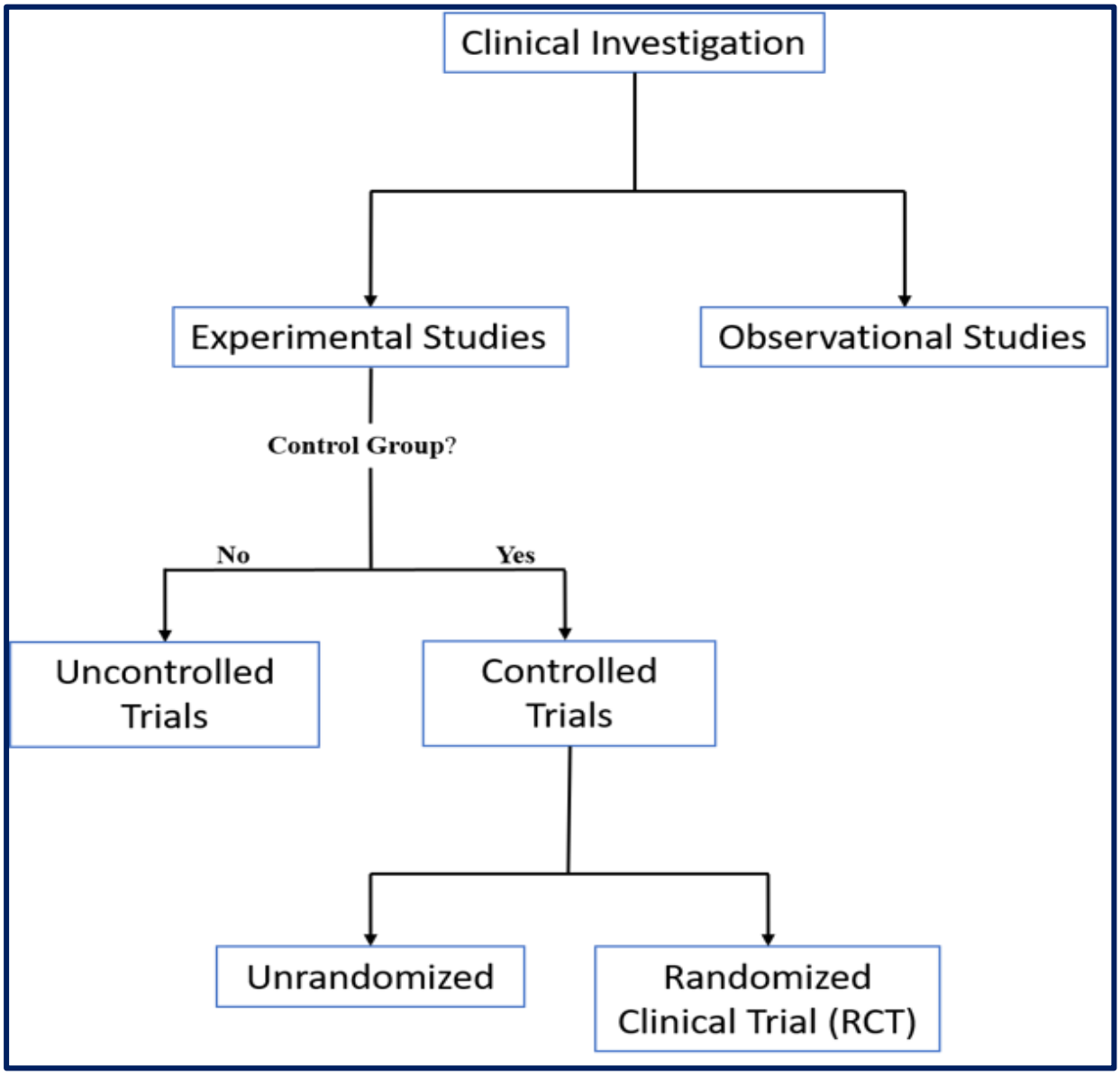

Figure 1. Clinical Research Hierarchy

i) Randomized Clinical Trials

The clinical trial has become the “gold standard” of every clinical investigation because it is “the most definitive tool for evaluation of the applicability of clinical research” and signifies “a key research activity with the potential to improve the quality of health care and control costs through careful comparison of alternative treatments”. A clinical trial can be defined as a

randomized controlled clinical study that follows a prospective timeline to evaluate the efficacy and validation of intervention(s) when compared to a control. (15)

A “traditional” clinical trial has four methodologic distinct phases, numbered from zero (0) to five (IV) (Figure 2.) In this review, it will only be considered the RCT of experimental drugs, and not experimental medical devices. In the European Economic Area (EEA), “approximately 4,000 clinical trials are authorised each year. This equals approximately 8,000 clinical-trial applications, with each trial involving two Member States on average.”. (16)

Phase 0 trials (Exploratory Studies), from the clinical point of view, represent the first administration of the experimental drug to volunteer participants. Being the preliminary assessment of the safety that it represents; micro dosages are administrated to a very small group of healthy volunteers.

Phase I trials usually rely on a small group (proximally 20-80) of healthy volunteers and patients to who all standard therapies have already been given and showed therapeutic inefficacy in their specific clinical panorama. Crescent dosages of the ED are administrated, until the maximum tolerated dose is reached, to the volunteers in order to continually test the safety of each dosage.

Pharmacokinetic (e.g. compartmental distribution levels and bioavailability) and pharmacodynamics phenomena are described in this phase, alongside with the primary assessment of ED activity. This phase usually has a duration inferior to one year, and 50 to 70% do not meet the necessary criteria to progress to the PT-II. Phase I cancer clinical studies are not performed in healthy patients since the risk/benefit equation would not be favourable to them. Patients, in the previously described clinical panorama, are usually enrolled through volunteer participation, as a “last therapeutic resort”. (17)

Phase II trials (PT-II) focus is the characterization of ED biologic activity and the corresponding clinical effect. In the previous phase, the dose or range of doses have already been defined, but different doses of the ED (beneath the minimal therapeutic dose limit) may be administered to infer the dose-response relation. In terms of enrolment, patients are recruited (proximally 50-200) by the Principal Investigator (PI) according to the inclusion and exclusion criteria. PT-II often includes more exclusion criteria and more specific inclusion criteria, when compared to the next phase (PT-III). Its duration often revolves around the two years mark, and only a third of the ED advance to the next phase (PT-III). (17)

Phase III trials are multicentric explanatory studies, designed to assess the efficacy/effectiveness of the new intervention in a largely homogeneous population (typically, 100 to 1000 patients). Safety and dose-response relation continues to be an important focus,

accompanied by ridged inclusion and exclusion criteria. Patients enrolment follows the same rules as previously reported for PT-II. Ideal dose or range of doses, described in previous phases, are applied. Depending on the study design, in order to best suit the scientific, legal, and ethical requirements, different groups and randomization processes are applied. This often relays on two distinct randomized groups where the new intervention is compared to the standard intervention plus/or placebo. A second period, defined according to the protocol, predicts a follow-up period in which the patients continue to be followed by the clinical team in charge after the end of the new intervention administration. (17)

Phase IV trials, the studies promotor applies for a commercialization authorization, vary according to the legal requisites of the country(ies) the permit will be applied. Only new interventions that demonstrated safety and effectivity, according to specialist's evaluation, and promising results in all non-clinical and clinical studies are approved by the regulatory agencies. Commercially approved drugs continue to be closely evaluated in terms of effectiveness and safety (e.g. adverse reactions) through Pharmacovigilance Agencies. (17)

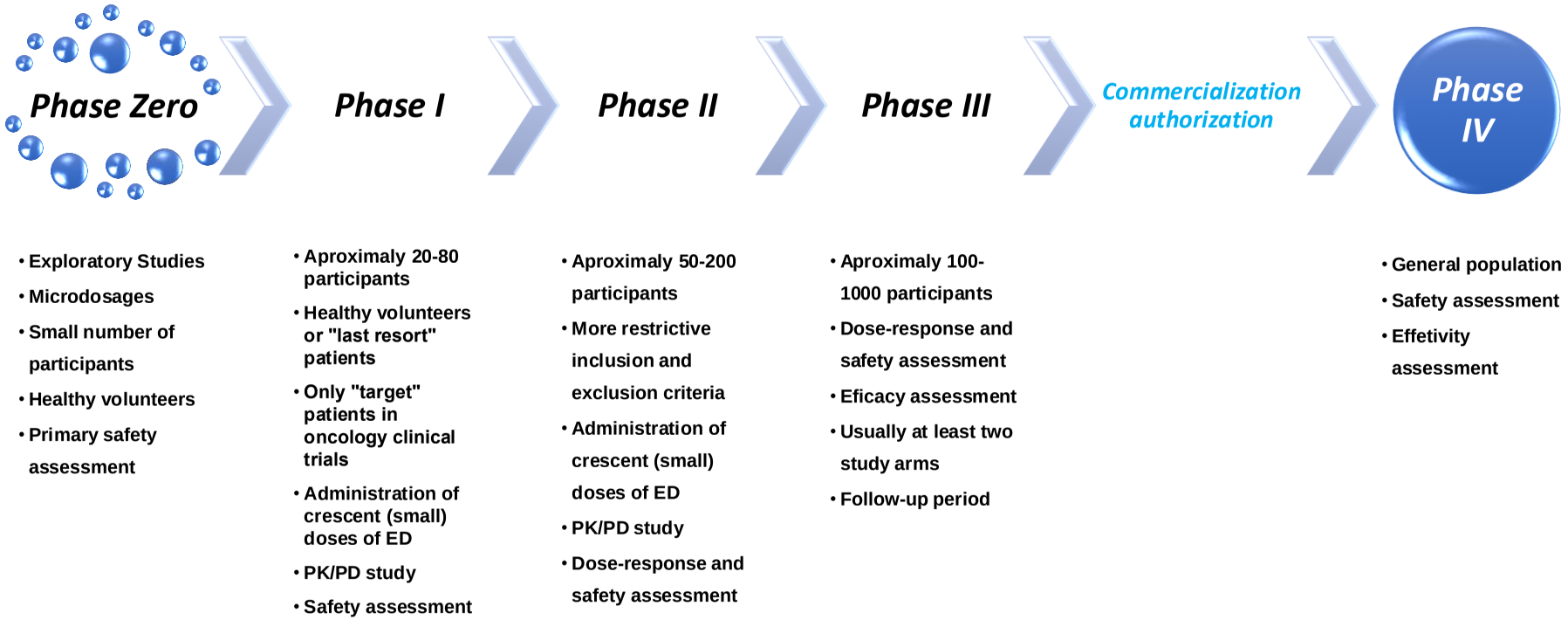

Figure 2. Phases of a clinical trial

5. Ethical Theories

Ethical Theories were formed along the centuries in order to try to assess the best course of moral action according to several different principles. Although the definition of “right” and “wrong” may differ according to the cultural principles of each individual society and individual morals and believes, some theories have been able to grasp different, and at the same time complementary, views and construct principles according to such phenomena.

Consequentialism is deeply rooted with the social views of John Stuart Mill in which the benefit of the majority outweighs the benefit of the minority. Such strand applied to the clinical domain forms a theory in which the consequences of an intervention attribute “moral credit” to the intervention. In other words, what is considered ethical is the procedure that originates benefits, and deemed unethical if it is the principle that causes prejudice/harm. (18)

Deontology comes from Immanuel Kant, in which the focus is on the action itself, and indices that each person has more obligation towards another, and their actions are ethical if they accomplish them according to their obligations. (18)

Virtue ethics, on the other hand, focus on the individual characteristics of the intervention´s agent, which is translated in a definition of what is ethical and what is unethical according to the virtue of the individual applying the intervention. (18)

Normative ethics is not in itself a different theory but the cooperation of the previous three theories since they complement themselves. It implies that the goal of every individual is to practice actions deemed “good”, with the consciousness of the consequences of their acts, both on a personal and a social level. (18)

6. Ethical Principles

Ethical Principles (Table II.6.) are a product of the previous ethical theories, summarizing the core principles in which all individual and social conduct should oblige, within the realm of logic. The four core principles applied to the medical sciences are the respect for autonomy, beneficence, nonmaleficence and justice. (18)

Three ethical principles rule all medical acts, and all health professionals are obliged to stick to their full extent, and they can be defined as Beneficence and Non-maleficence, which state the responsibility of acting according to the patients best interests in order to achieve the best outcome possible with no, or the minimally necessary, harm; Respect for Autonomy, translating in the involvement of the patients in their own medical decisions through carefully transmitting the needed information so that a well-based decision can be made by them, and prosperously respecting such decision; Justice, meaning the act of being fair in any decision while balancing the interests of different people involved in the medical process.

The principle of **respect for autonomy** entices that the patient has the right to make decisions concerning its own life regarding he is self-aware of the consequences of their actions and free of any coercion (e.g. refuse treatment).

The principle of **beneficence** entices the medical act to be towards the participant best interests (most benefice).

The principle of **nonmaleficence** points towards the avoidance of causing harm, applying to any individual participating in the “medical care circuit” (physicians, patients, and other health care staff).

The principle of **justice** determines that regardless of the social and economic background, every individual has the right to be treated equally and the limited resources must be equally distributed. In regards to medical sciences, it is applied the concept of clinical equipoise, representing the principle of justice directly conceptualized into the medical act/care.

Other two ethical principles have started to be defined as a direct consequence of the four-core previous stated, those being the principle of noncoercion and nonexploitation.

The principle of **noncoercion** induces that no external force influences the patient’s own decisions.

The principle of **nonexploitation** entices that the actions of third parties do not act according to their own best interests while desecrating any other of the previous principles.

Clinical equipoise entices the principle of justice focused on the fair distribution of resources available during treatment or research in a fair and equal method. It can be described as a principle that translates in equal treatment for all individuals regardless of socio-economic factors. Given an example, in an RCT it is expected that there is no better treatment for either one of the study's arm (control and experimental group(s)). (19)

As another side of the same coin, equipoise towards individual moral conduct, **personal equipoise**, entices the behaviour of a health care provider regarding the clinical and research practice in which the individual cannot have any bias towards treatments/patients preference or doubts about the risk and benefit assessment of the treatment applied in either domain. Although the western society is driven towards the full application of such principles, the economic and social reality may not permit it, but also the own interaction between principles can originate paradoxes in which no consensus exists or is possible to achieve. For instance, the principle of autonomy may conflict with the principle of beneficence, when the intervention that the physician deems beneficial or even essential is refused by the patients.

Table II.6. Summary of the Ethical Principles

Ethical Principles	Summary
Respect for Autonomy	The self-government of own decisions
Beneficence	Act according to patients' best interest
Nonmaleficence	Avoidance to cause harm
Justice	Equal distribution of resources
Secondary Principles	
Noncoercion	No external force affecting one's autonomy
Nonexploitation	No manipulation to archive second- or third-party interests
Clinical equipoise	Equal distribution of clinical/research resources (equal treatment)

7. Ethics and Clinical Research

Clinical research cannot be conducted without the full extent application of the ethical principles that rule the clinical practice. In other words, ethical principles represent the main building block of any design and conduction of clinical research.

Starting with the atrocities committed in the Nazi concentration camps, in the name of scientific progress, the necessity to create not only legal requirements to the design and conduction of clinical research but also ethical obligations/recommendations was raised. The ethical fundaments assure the well-being of the participants while maintaining the scientific value needed to assure the intended results. In other words, clinical research "should answer important public health questions without impairing the welfare of individuals." (20)

Different ethical guidance documents have been elaborated by several organizations in order to harmonize the design and conduction according to the ethical principles that are applicable in each individual case.

Over the last years, accompanied by the fast-passed scientific progress, new challenges have arisen in the DCCR. Such challenges created "tremendous controversy surrounding the ethics of clinical research.", which implies the constant need for improving the ethical principles to cover every single patient subjected to clinical research. (21)

8. Ethical Guidance for Clinical Research

Clinical research ethical requirements are formulated according to the necessity to resolve a previously encountered situation of controversial ethical phenomena, in order to avoid its repetition, or according to a prospective necessity. “Ethical requirements for clinical research aim to minimize the possibility of exploration by ensuring that research subjects are not merely used but are treated with respect while they contribute to the social good.” (22) The most reliable and consulted guides to ethical conduction in clinical research “have been the Nuremberg Code, Declaration of Helsinki, The Belmont Report, International Guidelines for Biomedical Research Involving Human Subjects, and similar documents.” (22)

i) Nuremberg Code

“The Nuremberg Code drafted at the end of the Doctor’s trial in Nuremberg 1947 has been hailed as a landmark document in medical and research ethics.” The aforementioned publication is considered by many as “the most authoritative legal and human rights code on the subject of human experimentation”. Its creation represents a response to the ethical atrocities committed in the clinical experimentations developed in Nazi concentration camps. General Purposes of the Nuremberg code focus “on the need for consent and a favourable risk-benefit ratio but, on the other hand, fails to discriminate topics as “fair subject selection” and independent peer-review. The Ethical Principles defined in NC can be found in Table II.7 (23)

Ravindra B. Ghooi, in his critique article on the Nuremberg Code, fundaments the resemblances between the NC and the previous Guideline for Human Experiences in 1931. Such guidelines were based on the Berlin Code 1900 that was released by the Prussian Government, the first of his kind. (24)

Nº	Table II.7. Ethical Principles in Nuremberg Code
1.	The voluntary consent of the human subject is absolutely essential.
2.	The experiment should be such as to yield fruitful results for the good of society, unprocurable by other methods or means of study, and not random and unnecessary in nature.
3.	The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.
4.	The experiment should be so conducted as to avoid all unnecessary physical and mental suffering and injury.
5.	No experiment should be conducted where there is an a priori reason to believe that death or disabling injury will occur; except, perhaps, in those experiments where the experimental physicians also serve as subjects.
6.	The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.
7.	Proper preparations should be made and adequate facilities provided to protect the experimental subject against even remote possibilities of injury, disability, or death.
8.	The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.
9.	During the course of the experiment, the human subject should be at liberty to bring the experiment to an end if he has reached the physical or mental state where continuation of the experiment seems to him to be impossible.
10.	During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

ii) Declaration of Helsinki

The “Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects” is an effort of the World Medical Association and was first adopted in 1964 and “is arguably the most widely known and influential guideline in medical research worldwide.” Its recognition has granted it a status above national legal and policy affairs, granting it a significant authority. Continuous revisions have been made in order to update it according to the rise of specific necessary ethical guidance. The last revision was made in October 2013 at the General Assembly in October 2013. Its main purpose is “attempting to define the moral status of clinical research, the importance of balancing risk and benefit to subjects and to society, the role of informed consent, and the importance of considerations of justice for patients, subjects, and populations”. (21) The main weakness of the DH is its room to interpretation that can result in polemic and incoherence outcomes. (25) The years of publication and revision of the Declaration of Helsinki can be found in Table II.8.

Table II.8. **Declaration of Helsinki** ***publication data***

	VERSION YEAR
DECLARATION OF HELSINKI	Version 1964
	Version1975
	Version 1983
	Version1989
	Version 1996
	Version 2000
	Version2004
	Version 2008
	Version 2013 (OCT)

iii) Other Declarations

The “WMA Declaration of TAIPEI: Research on Health Databases, Big Data and Biobanks” main goal is to protect “the rights of individuals giving their tissue or data for research and other purposes based on confidentiality and privacy rules”. This Declaration works in synergy with the HD, complementing the last, by being specific in addressing “any use of health database and biobanks excluding individual treatment”. There is no specification on clinical research,

being all principals applied to the general health, in contrast to the HD exclusivity to clinical research. (26)

“Declaration of Geneva: The Modern Hippocratic Oath” is a policy adopted by the World Medical Association (WMA). This document is synergic with the International Code of Medical Ethics and should be read concomitantly. The years of publication are expressed in Table II.9. (27)

Table II.9. **Declaration of Geneva *publication data***

	VERSION YEAR
DECLARATION OF GENEVA	Version 1948
	Version 1968
	Version 1983
	Version 1994
	Version 2005
	Version 2006
	Version 201? – (Public Draft – April 2017)

WMA Declaration of Tokyo consists of “guidelines for physicians concerning torture and other cruel, inhuman or degrading treatment or punishment in relation to detention and imprisonment”. (28)

iv) The Belmont Report

The Belmond Report was published by the National Commission for the Protection of Human Subjects of Biomedical and Behaviour Research, in 1987, and comprehends the core moral and ethical principles in clinical research. The core principles can be categorized in three domains, applied in a research context: “respect for persons applies to informed consent, beneficence applies to risk-benefit assessment and justice to the selection of research participants.”. (29)

v) International Ethical Guidelines

The International Ethical Guidelines for Biomedical Research Involving Human Subjects from the Council for International Organizations of Medical Sciences. The council was created, in 1949, by the World Health Organization (WHO) in conjunction with the United Nations Educational, Scientific, and Cultural Organization (UNESCO). Their referent guidelines describe the recommended ethical conduction of clinical research, through a series of specific topic-related publication. Given an example, guideline 1 refers to the need for any clinical study involving human participants to have a scientific background to ensure its benefit and relevance and be ethically correct. Guideline 2, on the other hand, lies on the constitution and conduct of review ethics committees. Continuous efforts have been made by the two agencies in order to improve their guidelines and make them accessible (e.g. several languages) and applicable to a global framework. (30)

vi) National and Transnational Bioethics Committees

The arise of ethical principles and its implications lead to the creation of consultative organs capable of reviewing and issuing scientific advice about a biomedicine matter. In this context, bioethical committees were created, constituted by a group of selected specialists with previously demonstrated qualification to this office. The committees can have a local domain (e.g. a central health care facility), national domain if their advice impacts at a “country level”, or lastly can also function in an international level in which the decisions impact a range of countries. At a clinical research level, they represent an essential part, reviewing the study design and emitting ethical advice respectively, and assure the conduction between the ethical principles that CR is obliged.

vii) WMA International Code of Medical Ethics

The WMA International Code of Medical Ethics was published with the goal of harmonizing and summarizing the duties of physicians in general, towards the patient, and his colleagues. Different revised versions of this documented have been published, being the first in the year 1949, and the last revision published in 2016. (31)

Physicians are obliged to follow strict forms of conduct in order to assure the patient rights are respected and duties fulfilled, but also are his own and his colleagues’.

viii) ICH Guidelines for Good Clinical Practice E6 (R2)

Good Clinical Practice is defined as a standard of ethical and scientific excellence for “designing, conducting, recording and reporting trials that involve the participation of human subjects.” .This guideline purposes a unified standard applicable in the European Union (EU), Japan, and the United States in order to improve the concordance between the different regulatory authorities. (32)

Chapter III

Methods

III. Methods

1. Search strategy

According to the previously defined objectives of this work, the authors chose to develop a systematic review with a well-defined methodology to assess the most relevant publications.

In order to define the research question, the core eligibility criteria and the literature search, a "PICO strategy" – P (population); I (intervention); C (comparator); (O) Outcomes – was applicated (Table III.1.). The resulted research question was defined as: "*Which ethical constraints affect patients with psychiatric disorders in a clinical research context (compared to standard patient care / non-psychiatric patients)?*". To answer such question, the literature search and the application of the eligibility criteria was executed as demonstrated in the following sub-headlines, according to the defined "Pico strategy".

Table III.1. PICO Strategy

PICO	*DESCRIPTION*
Population (P)	Patients with psychiatric disorders
Intervention (I)	Clinical research
Comparator I	Standard patient care / Non-psychiatric patients
Outcomes (O)	Ethical constraints
	Research Question: Which ethical constraints affect patients with psychiatric disorders in a clinical research context (compared to standard patient care / non-psychiatric patients)?

2. Literature search

The literature search was conducted according to the Pull method – the hierarchical structure of literature evidence level (Pyramid of Haynes) – from the most to the least evidence. The search was conducted in three databases – UpToDate, PubMed and PsycINFO. The terms used in the three databases were the standard Mesh (controlled language) terms defined in "MeshBroswer" – "Psychiatry", "mental disorders", "research" and "ethics" – and used in different query's using Boolean operators – "AND", "OR" and "NOT".

3. Eligibility Criteria

The criteria defined for the eligibility assessment of the article's inclusion is applied according to the investigational question defined by the PICO strategy. The application of the eligibility criteria in the primary identified publications, consisted in three sequential assessments (Table III.2.) – title Assessment, abstract assessment and full-text assessment – refining the included articles adequacy to the PICO strategy and other criteria previously defined by the authors.

Table III.2. Eligibility Criteria

Domain of Application	Inclusion Criteria	Exclusion Criteria
Title Assessment	Topic related	Off-topic
	Publication date: 2000 to present	Publication date before the year 2000
	Human species	Other Species then Human
Abstract Assessment	Suitability w/ PICO criteria	Unsuitable w/ PICO criteria
Full-text Assessment		

The full publication´s eligibility assessment as executed as shown in the following flow chart (Figure 3.).

4. Flowchart

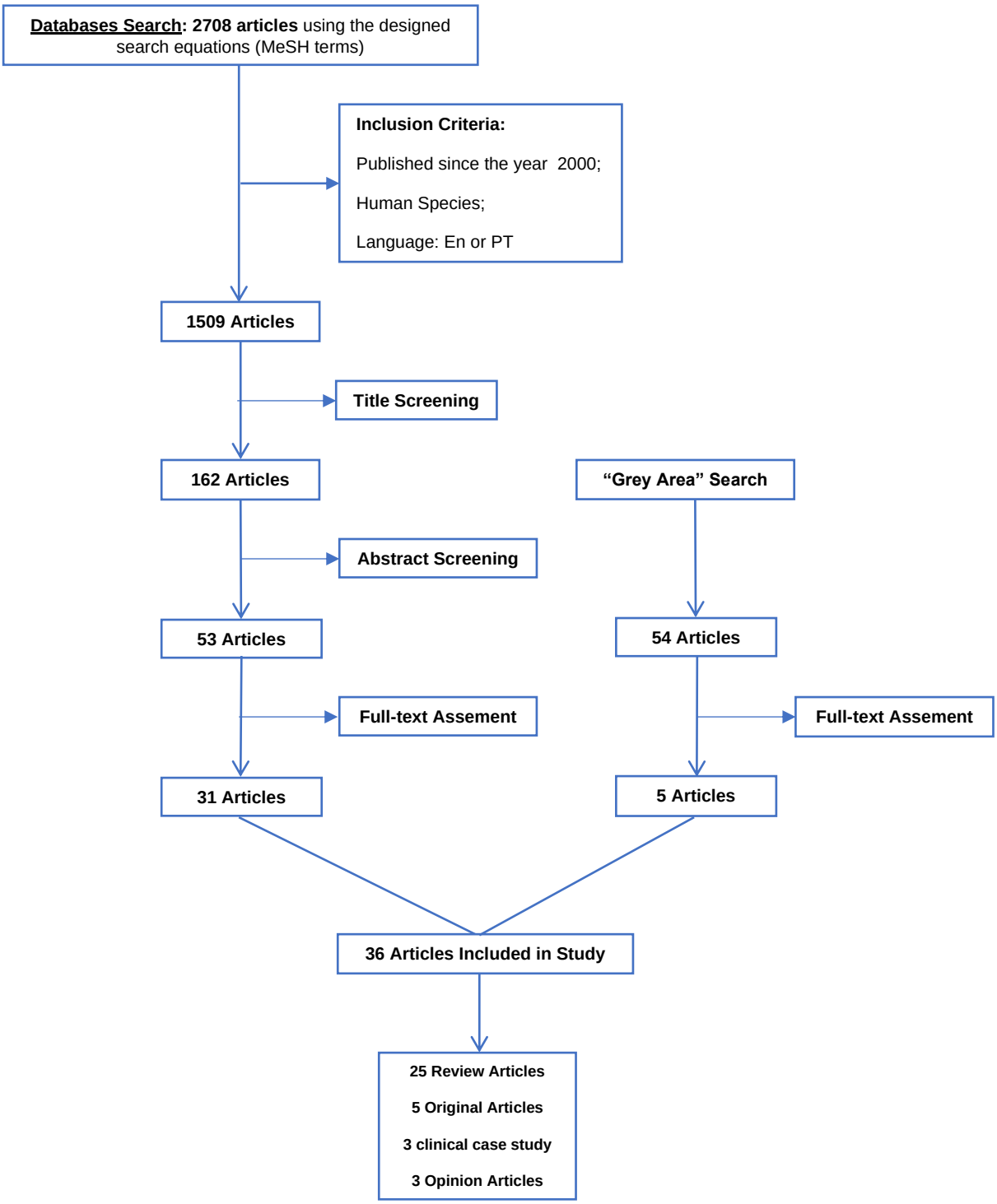

Figure 3. Flowchart of the study's methodology

Chapter IV

Findings

IV. Findings

The search strategy presented a total of one thousand five hundred and nine [1509] publications from the selected databases (PubMed and PsycINFO). The application of the previously defined eligibility (inclusion and exclusion) criteria resulted in the inclusion of a total of thirty-six publications deemed of interest by the authors. The publication type of the included articles was assessed as twenty-five review articles, five original articles, three clinical case study and three opinion articles.

The included articles were analysed, and their information summarize according to the study´s population, objective, methods/results and the main ethical concerns discussed, as shown in Table IV.1.

Table IV.1. Summary of the included articles

YEAR	AUTHOR	JOURNAL	POPULATION	OBJECTIVE	METHODS & RESULTS	ETHICAL CONCERNS DISCUSSED
Review Article						
2018	Hokke *et al.* (33)	PLOS|one	General population	Review the evidence of ethical issues reported in the use of online clinical research methodology	65 articles included + 15 guidelines (5 professional and 10 universities) of 3794 identified articles from the several databases – Scopus, Cinfo, Embase, ERIC, CINAHL and Informit – and other sources	Informed consent High-risk populations – paediatric Privacy and confidentiality
2018	Anderson *et al.* (34)	Therapeutic Innovation and Regulatory Science	Psychiatric population: Substance use disorder	Review and discuss the ethical issues affecting the substance use disorder research	Undisclosed	Informed consent Decision-making capacity & Cognitive impairment Financial incentives Threats to voluntariness
2017	Carrier *et al.* (35)	Progress in Neurobiology	General psychiatric population	Review and discuss the ethical challenges in psychiatric drug development	Undisclosed	Randomization Placebo-controlled trials Endpoints

						Active comparator Funding Suicide risk High-risk populations (paediatric, geriatric, neonatal and prisoners)
2017	Prusaczyk *et al.* (36)	Clinical Gerontologist	Nonpsychiatric population: Cognitively impaired	Summarize and discuss the clinical implications of the informed consent application in research on cognitively impaired populations	Undisclosed	Informed consent Decision-making capacity & Cognitive impairment Exclusion from research
2017	Spencer *et al.* (37)	Psychological Medicine	Psychiatric population: Schizophrenia	Review the evidence of the association of DMC and social and psychopathologic factors in schizophrenia and related diseases	Publications deemed relevant by the authors and according to the defined eligibility criteria from the following databases: Embase, Ovid and PsycINFO	Decision-making capacity (treatment and research) & Cognitive impairment DMC assessment tools
2015	Humphreys *et al.* (38)	Journal of Psychiatric Research	General psychiatric population	Assess and discuss the psychiatric exclusion criteria phenomena in the most contemporary relevant clinical trials for prevalent chronic disorders	Collection and analyses of exclusion criteria in 400 clinical trials [20 trials of each 20 most prevalent chronic disorders]	Exclusion criteria Principle of Justice

2014	Jonsson *et al.* (39)	Contemporary clinical trials	General psychiatric population	Assess the adverse events report across clinical studies and discuss the resulted data regarding monitoring and methods to collect/report adverse events	132 trials included of 3696 articles identified [2010] from PubMed and PsycINFO	Reporting and monitoring adverse events in RCT
2014	Bagarić *et al.* (40)	Psychiatria Danubina	General psychiatric population	Review and discuss the procedural challenges in informed consent use in research and treatment	Undisclosed	Informed consent Decision-making capacity & Cognitive impairment
2013	Hindmarch *et al.* (41)	BMC Medical Ethics	Psychiatric population: Depression	Review empirical and clinical ethical accounts on how depression affects DMC.	17 articles included of 1585 identified publications.	Informed consent Decision-making capacity & Cognitive impairment
2012	Groisman *et al.* (42)	BMC Medical Ethics	Psychiatric population: Bipolar disorder	Review of the use of next-generation sequencing technologies in bipolar disorder.	217 studies included in PubMed.	Informed consent Benefit: Risk ratio Participant protection Decision-making capacity & Cognitive impairment
2012	Alphs *et al.* (43)	International Journal of Neuropsycho pharmacology	Psychiatric population: Schizophrenia	Discuss key issues related to the placebo-related effects and point solutions to diminish such phenomena	Undisclosed	Use and effect of placebo drugs

2012	Kitchen *et al.* (44)	Advances in therapy	Psychiatric population: Schizophrenia	Review the impact of cognitive impairment in schizophrenia and develop a conceptual model that permits to simplify such phenomena.	110 articles included of 3950 identified publications [January 1999 and November 2009] from the following databases: Medline; Embase; PsycINFO.	Decision-making capacity & Cognitive impairment (+ Humanistic and economic burden) Instruments to measure the impact of CI in schizophrenia
2011	Lysaght *et al.* (45)	Journal of Medical Ethics	Psychiatric population: Psychoses	Present the issues that researchers face in the decision to decide between the inclusion of participants with the risk of psychoses in a clinical study or allocation to treatment.	Undisclosed	Principle of clinical equipoise Participants recruitment Randomization
2011	Chong *et al.* (46)	Bioethics	General psychiatric population	Revaluate previously principles and practices in the field of psychiatric research	Undisclosed	Informed consent Decision-making capacity & Cognitive impairment
2011	Striley *et al.* (47)	Current Opinion in Psychiatry	Psychiatric population: Substance use disorder	Review the literature concerned with the ethics of international substance use disorder	Publications from 2009 to 2010 deemed “provocative and important” by the author.	Financial incentives Recruitment Stigmatization Respect for autonomy
2010	Helmchen *et al.* (48)	European Archives of	General psychiatric population	Literature review of publications (including	Undisclosed	Informed consent

		Psychiatry and Clinical Neurosciences		guidelines) concerning the ethics of psychiatry research		Principle of beneficence Benefit: Risk ratio Substitute consent
2010	Appelbaum *et al.* (49)	Current neurology and neuroscience s reports	Patients assessed with cognitive impairments	Review the effects of dementia and other cognitive impairments in the decision-making capacity to consent treatment and/or research, while assessing solutions.	Recently published articles deemed of interest by the author.	Consent to treatment Consent to research Decision-making capacity & Cognitive impairment DMC assessment instruments Substitute consent
2010	Kolch *et al.* (50)	Current Pharmaceutical Design	Psychiatric population: Paediatric	Review the ethical discussion around the paediatric population and the psychopharmacological treatment while considering research ethical guidelines changes and the need to update them according to recent developments	138 publications included from PubMed [2000 to 2010] and other sources + 4 European and American legislative publications	Legislative changes Informed consent Benefit: Risk ratio Study design Justice Conflicts of interest High-risk populations – paediatric
2009	Brandon *et al.* (51)	Current Opinion in Psychiatry	Psychiatric population: Perinatal research	Review and summarize the ethical panorama and challenges in	Current literature deemed relevant by the authors concerning the ethical	Current guidelines Fetal and maternal risks

				modern perinatal psychiatric research	panorama in perinatal psychiatric research	Conflicts of interest Therapeutic Misconception
2008	Tsao *et al.* (52)	Current Opinion in Psychiatry	General psychiatric population	Review and summarize the current literature of contributes to the ethics of psychiatric research	Current literature review from a wide range of core ethical subjects	Public perception Subjective Experiences Informed consent Observation studies Privacy & Confidentiality High-risk populations – paediatric Internet Communication
2004	Duval *et al.* (53)	Canadian Journal of Psychiatry	General psychiatric population	Review the ethical aspects/issues of psychiatric study design	Literature review and conceptual analyses of relevant publications focusing on study designs issues	Study design issues: Placebo-controlled studies Challenge studies Washout studies
2003	Fryers *et al.* (9)	Social Psychiatry and Psychiatric Epidemiology	General psychiatric population	Literature review of the evidence published linking conventional social markers and psychiatric disorders in developed countries	Literature review according to defined criteria. Inclusion of 9 studies, in which 8 presented favourable evidence.	Social inequalities Prevalence of psychiatric disorders

2003	Carpenter *et al.* (54)	American journal of Psychiatry	Psychiatric population: Schizophrenia	Review the position of the Declaration of Helsinki and further updates on the ethics of placebo-controlled trials, focusing on schizophrenia research	Review of the Declaration of Helsinki and the 2002 clarification regarding its position on the placebo-controlled trials in schizophrenia research	Declaration of Helsinki & updates Placebo-controlled studies
2001	Roberts *et al.* (55)	Comprehensive Psychiatry	General psychiatric population	Review and summarize the ethical framework of psychiatric research protocols	Undisclosed	Scientific value Research team Benefit: Risk ratio Privacy & Confidentiality Informed consent Decision-making capacity & Cognitive impairment Financial incentives Data publication Recruitment Peer review Exclusion criteria
2000	Emanuel *et al.* (22)	American Medical Association	General psychiatric population	Review and summarize the major ethical requirements for an ethical clinical study in all its domains (design,	Undisclosed	Social or scientific value Scientific validity Fair subject selection

		Special Communication		implementation and others)		Favourable risk-benefit ratio Independent review Informed consent Respect for potential and enrolled subjects
Original Article						
2017	Ostrow *et al.* (56)	Psychiatric Services	General psychiatric population Original article	Obtention of subjective personal clinical data about medication discontinuation and factor associated	Sample of 250 adults diagnosed with several mental illnesses and prescribed psychiatric medication for more than 9 months.	The proportion of medication discontinuation Subjective factors to discontinuation Respect for autonomy
2017	Hofer *et al.* (57)	Psychiatric Research	Psychiatric population: Schizophrenia	Assess and discuss the research´s drop-out rates of schizophrenia patients and their compliance in three domains: proportion (per cent), time (months) and reason	Inclusion of 194 schizophrenic patients (ICD-10), ages between 18 to 64, from 1997 up to 2010. Intervention: monotherapy with an oral new-generation antipsychotic Compliance assessment through interview and plasma levels analyses: baseline, weekly for 6 weeks, week 8 and monthly.	Drop-out rates Reasons to reduce to noncompliance

2010	Taylor *et al.* (58)	Journal of Nerves and Mental Disease	Psychiatric population: Schizophrenia	Research the subjective experience (feedback) of individuals diagnosed with a psychiatric disorder currently participating in a clinical study for psychoses and suicide	A sample size of 79 outpatients currently participating in a larger clinical study investigating the psychological factors that grant vulnerability to suicide	Qualitative analyses of the subjective experience Benefit: Risk ratio Minor ethical relations
2010	Adamis *et al.* (59)	Science and Engineering Ethics	Psychiatric population: Delirium research participants	Assess the DMC of psychiatric patients with delirium symptomatology. Discuss the implications and propose solutions to such matter	A sample size of 233 patients, aged 70 years or more, recruited within the first 3 days of hospital admission [July 2013 to April 2014]	Exclusion from research Decision-making capacity & Cognitive impairment
2006	Roberts *et al.* (60)	American Journal of Psychiatry	Psychiatric population: Schizophrenia	Summarize and discuss the subjective participant evaluation of risk in schizophrenia clinical research and its relationship with willingness to participate	Semi-structured interview of 60 schizophrenia research participants 4 harmful (symptom induction); 5 moderately harmful (placebo-controlled); 6 not harmful (physical examination)	Benefit: Risk ratio Placebo-controlled studies Challenge studies Willingness to participate

Clinical Case Study						
2015	Taylor *et al.* (61)	The American Journal of Bioethics	General population	Summarize and discuss a clinical research case in an ethics point of view	Case study of ethical analyses	Informed consent Decision-making capacity & Cognitive impairment Benefit: Risk ratio High-risk populations
2012	Millum *et al.* (62)	Journal of Nervous and Mental Disease	General psychiatric population	Create a collection of six case studies and their respective in-depth analysis.	Use of six available research studies that were proposed or carried out from around the world.	Informed consent Benefit: Risk ratio High-risk populations Ethical guidance
2009	Chen *et al.* (63)	Psychiatric Clinics of North America	Psychiatric population: Paediatric	Elaborate a practical guide of the ethical and practical considerations while performing psychiatric clinical research directed towards psychiatrists	Undisclosed	Research value & Scientific validation Investigator – Patient relation Therapeutic Misconception Informed consent Genetic research

Opinion Article						
2018	Lázaro-Munõz *et al.* (64)	Molecular Psychiatry	General psychiatric population	Identify and discuss improvements to manage the results return in clinical genomics research in psychiatry	Undisclosed	Arguments in favour versus against: - ethical principles - scientific factors - social factors
2016	Bracken-Roche *et al.* (65)	The Canadian Journal of Psychiatry	General psychiatric population	Discuss the core ethical principles and intrinsic vulnerability of the psychiatric population in a clinical research context	Undisclosed	Psychiatric population vulnerabilities Decision-making capacity & Cognitive impairment
2014	Huculak *et al.* (66)	Journal of Medical Ethics	General psychiatric population	Discuss the current scientific and ethic positions on the placebo effect and its use in treatment and research	Undisclosed	Use and effect of placebo drugs

Chapter V

Discussion

V. Ethical Issues in Psychiatric Research

The psychiatric population constitutes a highly vulnerable population that requires additional protection (legal and ethical) in order to assure their best societal and individual best interests, and the clinical research setting is no exception. Although many of the ethical issues that haunt medical research have been settled through numerous guidance's, most of them still do not present a clear solution and originate debate among the scientific community. In addition, the continuous progression of science has led to the conception of new issues that come into the debate (e.g. return of genomic results).

In clinical research, the psychiatric population is underrepresented by the common exclusion of this patient in major clinical trials. Although comorbidities, such as cancer and HIV infection, are as common, or even more so, in this population, they are still excluded by several exclusion criteria's that, in a partial or in totality, mean their exclusion from participating in clinical trials. The same problems can also occur in psychiatric research through the exclusion of some psychiatric disturbs while researching others. (38) Such fact creates underdevelopment in the clinical knowledge of psychiatric disorders.

The factors that create ethical paradigms or, at least, constraints in association with the lack of scientific knowledge regarding the psychiatric disorders will be extensively discussed in this review. This chapter will base its discussion from the previously stated contemporary knowledge (Chapter II – Theoretical Fundaments) in association with the data collected from the publications included in this review (Chapter IV – Results).

This chapter will focus on the ethical constraints intrinsic to the clinical research design and conduction in psychiatric participants in association with those that are multidimensional across the entire clinical research. A focus will be given to the randomized clinical trials ethical issues since they englobe the majority of the topics discussed in this review. Schizophrenia and depressive disorders will be used as illustrative examples of the ethical issues assessed in pathologies of psychiatric indole. A general approach will be given at the beginning of each chapter in order to contextualize each major issue, individually.

The flow of the topics discussed will be partially based on the special communication, from the American Medical Association, which proposed seven requirements for ethical clinical research: Value; Scientific validation; Fair subject Selection; Favourable risk-benefit ratio; independent review; Informed consent; Respect for enrolled subjects. (22)

1. Research Value & Scientific Value

Research value is the figurative representation of the social benefit that can outcome from the research. In other words, it is the attributed significance of a clinical study regarding the impact of the gained knowledge on science and public health. In practical terms, research value translates to an evaluation of the possible knowledge gain versus the burden of the research protocol. For a study research value to be deemed ethical, it is needed that the gained knowledge represents a significant scientific and social benefit. In cases where the results produced are not applicable to a broad spectrum of patients or simply will only contribute to increasing the validity of a previously well-validated hypothesis or intervention, such study cannot be considered ethical. (22)

In contrast, the **scientific value** can be defined as the representation of the attributable value of the scientific principles and procedures inserted in clinical research. In practical terms, in order to deem a clinical study protocol ethical, it has to rely on well-accepted and validated scientific principles, methods, and practices, in order to produce reliable results. (22)

The clinical research for psychiatric disorders has been for several decades as one, if not the most, scientific rigorous due to the additional risk posed for its participants. (55) The estimated ratio between benefit and risks of research is only justified by potential contributions to the scientific, social or clinical panorama. A physician, or in this case a psychiatrist, should accept to conduct research in the site he is affiliated only when in it goes in accordance with his personal judgement, the risks are justified by the potential contributes of the research and the protocols are scientifically valid and appropriate in a social and clinical panorama. (63)

The **principle of justice** comes in deep intricacy with both types of attributable value (research and scientific). The funds from the study sponsor are empirically finite, and its abuse leads to the misuse of such funds that could have been used in other research or another scientific purpose, with a greater scientific or social benefit. In the case of the **principle of nonexploitation**, this relays on the exposition of patients to possible harm without any benefit in perspective. (22)

2. Participant Selection and Recruitment

Participant selection and recruitment entices the choice and subsequent enrolment of patients in clinical research according to defined eligibility (inclusion and exclusion) criteria, and the protocol adopted to recruit such individuals. In the study design, beyond the previously referred aspects, the potential populations intended to participate are well scrutinized.

In the first instance, for a research protocol to be deemed ethical in his participant selection, it must ensure that in order to achieve the proposed goal, the ethical principle of **Justice** is not deteriorated. This can be translated in enrolment criteria that does not include vulnerable patients in the context of high-risk experimentation, but if their inclusion is deemed necessary, the benefits have to meet the potential benefit to that specific population. (21,22,67)

In study's protocols, it is often found exclusion criteria that inhibit psychiatric patients to participate in clinical research, mostly in clinical trials, and consequentially takes away the advantages that might be produced by their recruitment. In the case of non-psychiatric trials, for example, the exclusion of psychiatric patients from participating, may result in the use of a drug to treat a certain condition and that is going to be prescribed and/or used by the psychiatric population, even though there are not any data supporting the action and effect of determined drug regarding the synergy with the specific pathology of such group of individuals. Another consequence comes from the exclusion of this population from research towards psychiatric disorders, motivated by the inclusion of a population that suffers from only the target psychiatric condition, producing bias outcomes when translated to a heterogeneous population, since the psychiatric comorbidities are common on psychiatric patients. (36,59)

A study from *Humphreys et al.* aimed to assess the proportion of possible or definitive exclusion criteria present in the study´s protocol of a sample of four hundred clinical trials (400 RCT), including the top twenty most cited RCT of the twenty most cited medical conditions. The results showed that more than half of the sample size (219 trials) presented at least one definitive and/or possible exclusive criteria, being the RCTs focusing towards psychiatric disorders showed a higher rate of such criteria. According to the author, the most common exclusion criteria were associated with the following domains (presented in decrescent order of proportion): substance use disorder, concomitant psychiatric medication, psychotic episodes, suicidal ideology, and general psychiatric criteria. This data shows, even considering its limitations, a tendency to exclude psychiatric patients from research done, not only towards other non-psychiatric conditions but also trials from the same pathologic domain. (38)

This translates in a lack of experimental progression in the pharmaceutical and medical care directed to psychiatry patients. But also creates a void of information towards the relation

between psychiatric disorders/drugs and other drugs meant to treat nonpsychiatric pathologies (e.g. cancer), although such assessment would be possible through their inclusion in clinical studies. (38)

i) High-risk Population

High-risk individuals in research are those deemed, by physiological, social or demographic setting, more susceptible to harm or coercion. Although psychiatric patients are considered by themselves a high-risk group, the paediatric, geriatric, imprisoned and pregnant women populations inserted in the psychiatric population, show even higher associated risks.

(1) Children and Adolescents

The physiology of children and, to a lesser extent of teenagers, is not equal to that of an adult. Several body functions are in development translating in a substantial difference to adults, and even in between their population when comparing different age groups. In modern medicine, the pharmacologic treatment in the paediatric population relays on drugs mostly used without previous testing/studies supporting their use in this population.

Consent to research in paediatric individuals is much more complex then what is seen in other groups because these individuals lack the legal decision power and mental capacity to assess all the conditions and meaning regarding participation on a clinical study. Obtaining informed consent in this high-risk group requires a surrogate, in this case, a parent or legal guardian with a legal bound/power to give valid consent. The opinion of the child/adolescent may be taken into consideration if the individual shows evidence of mental capacity and maturity to give “judgement” regarding the matter of participating in research. (50)

Research on children and by the extent on adolescents is permitted, according to the European and American legislation, if it represents minimal risk and burden. The definition of the limits between minimal and excessive, considering both the risk and the burden, is a source of debate since different opinions emerge from different professionals. (50)

The return of individualized results in child and adolescent research is a topic of discussion when conducting research, not only in a psychiatric research setting but in all medical areas. The consideration of providing the results of research to parents or legal guardians comes from a perspective of giving a direct benefit to the participant, and not only conducting the research to provide scientific evidence that will provide social benefit. (52)

The inhibition of children and adolescents from participating in research towards their medical condition can be deemed unethical or an ethical failure since it results in a lack of knowledge in a group comparable with the adult age groups in terms of most conditions. This fact is exacerbated when considering psychiatric disorders since treatment for such conditions in this group ages are even more undeveloped considering the general panorama.

The following table (Table V.1.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.1. Illustrative Study Case I

A clinical study design proposed to assess the efficacy of already approved antipsychotic drugs (for adults) in children that possess a more than minimal risk.	
Ethical principles	**Justice** **Beneficence** **Nonmaleficence** **Clinical equipoise**
Ethical analyses	The use of antipsychotic, although not common, should be done with the support of clinical evidence obtained through clinical research. This statement is true, from an ethical perspective, regarding the benefits and justice/equipoise of such evidence. On the other hand, the principle of nonmaleficence entices the abolition, or at least the minimization, of harm. It is deemed unethical to expose children to risk higher than what is considered minimal, although definitions of what is considered minimal risk are still a topic of debate in the medical community. The study couldn't be conducted since it poses a more then minimal risk even if the evidence produced would potentially be of utmost benefit to the scientific community and, as a consequence, the patients.
Proposed solutions	• A solution would be a redesign of the study protocol in order to reduce the risk to an admissible level. If such would be proved as possible, the research could be carried out. Note: The procedure of consent should be applied as stated in the above discussion and taken into account the willingness of the child and the explicit consent of the legal guardian(s).

(2) Geriatric Population

The elderly population (age equal or superior to 65 years) represents a high-risk group in research mostly due to a high prevalence of cognitive impairments that affect the ability to give valid consent to treatment and research. This fact translates in an increased vulnerability regarding **exploitation** and **coercion**. As it may be, scientific research as to be done in such individuals since they represent a rapidly increasing demographic group with different physiological characteristics that translate, for example, in different pharmacokinetics and pharmacodynamics when compared with those phenomena's in the adult population (18 > adults < 65).

Special precautions must be met when facing the need to enrol such patients (competent adults do not provide the data needed to answer the research question) such as the designing of special education interventions that allow an "easier" approach to providing the necessary information and conditions for valid consent. (35)

(3) Imprisoned Population

Research on prisoners is one of the most discussed topics regarding high-risk individuals' participation in research. Due to previous abuses committed, in Nazi concentration camps, to prisoners for the gain of scientific knowledge, the Nuremberg trials ruled a number of factors to be taken in account when developing research in incarcerated individuals. (23)

Psychiatric disorders are very prevalent in imprisoned individuals which through an ethical perspective regarding the principal of **Justice/Equipoise** translates in a necessity of inclusion of such participants in clinical research. In order to be ethical, research on prisoners must be done with some particular protections, while taking in account the above general ethical principles, applied to all research and produce benefits (e.g. scientific knowledge) that affect the prisoners and the general population.

Research in prisoners present advantages such as fixated location (therefore are easily accessed/followed) and live in a highly controlled environment where variables such as diet and hours of activities including hours of medication intake are closely controlled. These advantages can lead to an unbalanced focus on research in prisoners since it reduces a lot of variables from the study and work by the study personnel. In spite of all the special characteristics of the imprisoned populations, they should have similar benefits and duties as the general population, and only certain special protections should be applied. The participation of a study should not directly affect the legal situation of the imprisoned individual

since the extra healthcare access and follow-up show be a sufficient benefit to personally benefit from their participation. (35)

(4) Pregnant Women Population

During pregnancy, the drug treatment has to take into account the unique physiology presented by women since, during pregnancy, the female individuals cannot be considered as an individual "unit". Before applying any drug to a pregnant woman, rigorous and scientific valid methods to assess the effects on the foetus and its development/health have to be applied in the first research steps. The fundamental investigation (in vitro) and animal research has to mandatorily assess the teratogenic potential of any drug in development before going to clinical research. Although psychiatric medication is not developed with the intention of being used in pregnant women, such can be deemed necessary when all the other alternatives have failed.

In an ethical perspective, an investigator has to respect the autonomy of the pregnant women but also has to make a careful decision regarding the best interests of the foetus since it is a dependent being, incapable of making an autonomous and conscious choice, that will suffer the consequences of the decisions of the first. This duality causes problems regarding medical treatment since what may be deemed beneficial for the mother may pose a severe risk to the foetus, or what is optimal for the unborn may represent a risk, through lack of treatment or undertreatment, to the mother. (35)

After the serious incident with the clinical trials for "Thalidomide", the clinical research regarding pregnant women has focused on the risk of teratogenic effects of the drugs, but in psychiatric research, the focus is shifting towards the molecular effects of such drugs in the neuro-behavioural development of the foetus. The potential effects of antipsychotics and other psychiatric medication, including antidepressants, on the molecular level, is still unachievable with the modern technology capacities, which translates in a gap in knowledge regarding the neurologic and subsequent behavioural effects at long term in infants that have been subjected to such medications while still in the womb. (35)

ii) Drop-out rates

Study's dropout is a common phenomenon in clinical research, being its rates higher in clinical trials. In psychiatric research, the previous statement becomes exacerbated, being among the highest dropout rates amongst the different medical specialities.

Hofer *et al.* conducted an observational trial to assess three major factors – dropout rates and reason, symptoms and medication side effects, compliance – in individuals with schizophrenia (according to the ICD-10) and in monotherapy with an oral antipsychotic (the new generation that not clozapine). The time to dropout was assessed in four different periods and found that around thirty per cent (30%) of the participants abandon the study in the first month and again during the second/third month, contrasting with the twelve to sixteen per cent (12-16%) of the other two periods, four to six and seven to twelve. In relation to the motives of dropout – "poor response", "non-compliance", "side effects", "suicide", "withdrawal of written consent and logistic reasons" – the percentages varied between around fourteen (14%) and thirty (30%) percent, except "suicide" and "logistic reasons" that minted rates around zero point six (0.6%) to four percent (4%). The results also showed a decrease in the symptomatic severity and drug side effects in the participants that completed the study when compared to those who dropped out. (57)

3. Financial incentives

Financial incentives to researchers and participants are a commonly debated theme regarding the ethical values that enter in conflict since such phenomena may lead to erratic participants enrolment. In terms of physician´s payments, if the financial value surpasses the amount considered necessary to stimulate their efforts, and reward them for their time and effort, it may lead to excessive and erratic selection and recruitment of individuals that don't meet the ethical and safety requirements deemed necessary for such participation, although the inclusion criteria are meet and no exclusion criteria is.

On another hand, the payment regarding the participants is mainly based on financial compensation to cover any expenses that they might have had in their participation (e.g. trips made to the research site in order to attend to the periodic consultations). In the specific case of Phase I clinical trials, payment may be higher regarding participation, covering not only the expenses that came from their participation but also "rewarding" their time, effort and risks taken. It is implied that the financial incentives should be balanced according to such factors – time spent, efforts made, and risks engaged.

Financial compensation for the time expended, effort and potential inconveniences or risks can be deemed ethical if done in a fair proportional amount since it entices participation in research turning the research protocol more feasible. (55)

The attribution of high financial compensation, beyond the deemed fair value, is considered unethical because it may lead to imprudent and dangerous decisions regarding volunteer participation. Independently of the participation of healthy volunteers or patients, the amount given should never be as high as to entice risky participation, in other words, it should never entice participation without a proper uninfluenced decision. (20,21) A potential method of reducing such bias may be an explicit interview where the motives for participation are explored as well the impact of the financial compensation may have on the individuals. (55) On the other hand, those with financial and influence power should never be privileged in the enrolment for probable benefit research.

The implications of financial incentives in psychiatric disorders such as the opportunity for coercion and exploitation represents a major ethical issue when developing a psychiatric clinical trial. Evidence shows a higher prevalence of psychiatric disorders in individuals with lower incomes. Such ethical issues created from the positive association between financial capacity and the prevalence of mental health issues have yet not been fully reviewed. (52)

Additional precautions concerning financial incentives need to be taken when designing a psychiatric study since the participants may include low-income individuals that may be willing to participate without a fully informed and pondered decision since their participation can translate in an extra income, earned by participating. Some psychiatric disorders such as those characterized for substance use disorders, the money received from their participation in research may be used for self-harm, as feeding their own addiction. (34)

The following table (Table V.2.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.2. Illustrative Study Case II

A clinical study aimed to assess the effects of drug abuse treatment in schizophrenic patients being treated with, at least, one antipsychotic. The study predicts an avulsed financial compensation above the amount deemed proportional to participant time/effort spent and risks underwent.

Ethical principles	**Nonmaleficence** **Justice**
Ethical analyses	According to the principle of Justice, financial compensation, in a proportional amount, is fair since the participants spend time and effort while taking potential risks that can outcome from their participation in research. A not proportional amount of financial compensation can, not only produce erratic participation in research for financial gain, but also such income can be misused resulting in the harm of the participant. Such case is very important while conducting research in drug users since the money can be reverted to their addiction. The research protocol couldn't be deemed ethical and be approved by peer review or the ethics committees since the financial incentives surpass what is deemed fair and can contribute to the harm of the participants, and the risk of the study's income being reverted to continue the drug abuse can't be fully eliminated.
Proposed solutions	• Reduce the amount of financial compensation to levels deemed fair (proportional to participant contributions); • Periodic drug tests to assess the nonexploitation of the money received from their participation.

4. Risk-Benefit Ratio Assessment

Clinical research can be defined as an experimental and exploratory study of a hypothesis or intervention in which limited knowledge exists. Such studies represent an inherent risk of harm alongside with the potential individual and social benefits through the scientific knowledge obtained. In order to be possible to deem a clinical study ethical and proceed with its implementation, the individual risk for participants may not surpass the potential benefit. In a first perspective, **risk-benefit assessment** serves as a theoretical value attributed to the relation between the risk's participants are subjected and the potential benefits that may come from such research. It aims to predict, to the full possible extent, the ratio of such variables, and only when the main clinical and ethical conditions are fulfilled, a clinical study may be conducted.

Emanuel et. Al. defined three main concepts to assess such feasibility: "the potential risks to individual subjects are minimized, the potential benefits to individual subjects are enhanced, and the potential benefits to individual subjects and society are proportionate to or outweigh the risk". (22)

The study design should aim to accomplish to provide the best (beneficial) outcome feasible while causing minimal risks to the participants. In order to assure this feat, several aspects have to be deeply undertaken. When designing, the possible risks that may outcome have to be estimated and efforts have to be made in order to minimize them. Such efforts are made by carefully adapting the procedures, choosing those that uptake less associated risks and are best well known (e.g. standardized or well establish use assessed from high evidence literature) without prejudice to the study´s goals. Another aspect of such procedure choice goes through the enhancement of potential benefits that may outcome, in which the procedures have to be chosen in such a way that the best outcome from the design is obtainable.

Enrolment in research represents a variable inherent risk to participants according to the procedure(s) applied along with the study. In the particular case of clinical trials, given an example, the experimental drug may cause adverted adverse effects. Other cases such as those where there is a need to stop the medication, as in studies in which a placebo is given to the control group a placebo or a washout period are mandatory, can outcome in experiences of symptoms of withdrawal by the participants in different severities.

In psychiatry, the stopping of medication can result in relapses and dangerous behaviours such as suicidal ideation. Research conducted in poor populations may represent an increased risk since after the end of the clinical trial, even if the establish experimental therapy was

deemed effective, they may still not have access to the same treatment outside the trial. Other harms may come to the participants regarding the leaking of information regarding their participation in the clinical study, where they can be identified by a familiar member, friend, employer, or others, as to suffering from a determined psychiatric condition. (62)

The principles of Justice and clinical equipoise both come into play regarding this topic. In one hand, through the principle of justice, it is presumed that the study designs are conducted in such way that the funds and all the resources are equally distributed through all participants, translating in fair access to those resources by every single participant. On the other hand, the clinical equipoise translates in an equal treatment "quality" for every participant and the same potential individual risks and benefits from their participation in the study.

i) Suicide Risk and Management

Psychiatric disorders have an inherent risk of suicide that always needs to be taken into account both in the clinical practice and in research. In the conduction of research, it is mandatory the existence of management protocols that take into account such risk and define procedures in order to evaluate, prevent and manage the potential suicidal outcomes. The suicidal ideation is a common exclusion criterion in research justified by the increased need for "special"/individualized clinical care those individuals potentially need. Such fact originates a lack of understanding regarding not only suicidal ideation in a clinical level but also the knowledge of the effect of psychiatric drugs in these conditions. The current data regarding the effects of antipsychotic drugs in suicidal ideation and suicide are mainly assessed through observational studies which produce lower-level evidence when compared to interventional studies. (35)

5. Informed Consent

The informed consent is a requirement to any form of medical act, not only in general practice but even more in the clinical research setting. In terms of research, its main goal is to assure that the choice to participate in a clinical study is made based on a well-informed decision.

Kader *et al.* have defined the most important factors to consider, as a health professional, while asking a possible participant informed consent: awareness that the study is not being conducted to their individual benefit, but to the general benefit; if a placebo arm is present, the possibility of receiving placebo instead of the experimental intervention is essential to be well-established in the patient´s mind; any type of incentive to participation or coercion may not exist; patients can withdraw the informed consent at any time without any consequences to their health care. World Health Organization designed a template of informed consent to serve as a guide in the construction of such documents by different entities. (68)

Informed consent in psychiatric clinical research is the key point in safeguarding the process of obtaining an informed and voluntary decision from participants that were assessed sufficiently cognitive capable in order to allow a substantiated decision. (52)

In the psychiatric domain, the potential impairment of decision making-capacity leads to difficulties in the assessment of the cognitive capacity to make a well-informed decision when presented to informed consent. In psychiatric research, such patients may be unable to follow the cognitive steps – understanding the all the given study´s information; appreciate the information given; manipulate such information (reasoning); express their choice through acceptance of participation – that lead to their full capacity to sign the study´s informed consent. (69) Ethical issues regarding their participation arouse because without the proper cognitive analysis (e.g. SCoRS used in schizophrenia) there is no proper way of telling if the acceptance to participate comes from a well-informed decision or from pressure or coercion.

i) Cognitive Impairments and Decision-making Capacity

One of the biggest issues of the psychiatric population, regarding their participation in clinical research, is their cognitive impairment compared to mentally healthy patients, which evidence strongly shows to affect the functional outcomes of this population. The cognitive impairments can occur in several domains of cognition - attention, learning, somatic memory, working memory and executive functions. Given an example, in schizophrenia it is considered that almost all patients suffer from some degree of cognitive impairment, being sometimes argued its importance as a core schizophrenia symptom. Although their importance is largely debated,

it is not yet considered diagnostic criteria and no treatment has yet been discovered. (44) Several methods to assess the cognitive capacity in psychiatric patients have been developed, although they have little use in the daily clinical practice.

The “Decision-making Capacity” impairment is an effect of such cognitive deficits, and it represents the incapability to make a well-informed decision. In order to better understand this capability, four domains have been defined: Understanding, which represents the capacity of an individual to understand all information disclosing towards himself (conditions, risks/benefits of the intervention, amongst others); Appreciation represents the capacity to direct the understood information towards himself; Reasoning is considered the ability to manipulate information and develop a subsequential line of thought where all options are balanced in a rational way; Expression of choice is defined as the capacity to, in a clear and reliable way, communicate a choice. For a person to be deemed capable, all four different cognitive sub-domains must be present at the same time. (69)

Several tools have been developed over the years in order to assess the DMC, but they present highly variable outcomes due to the high subjectivity of the assessment and the assessor. This fact originates difficulties in establishing a pattern in which the application of such tools is enough to classify a patient as capable or not capable to make a well-informed decision, being the decision rested on the physician´s experience. DMC can be improved through cognitive training/stimulation, especially regarding the understanding and reasoning domains. The treatment of such impairment’s relays mostly on psychological and cognitive behavioural therapy, since the pharmacologic effect of the available drugs as little to no effect in the treatment of cognitive impairments. Cognitive remediation therapy shows high evidence in the treatment of cognitive impairments demonstrated by better cognitive and functional outcomes. (21)

From an ethical perspective, it can be deemed ethical the participation through valid informed consent, whether being obtained from the patient through “cognitively friendly” methods or surrogate decision making, when it presents minimal risk of causing harm. In cases where the risk is evaluated as more then minimal, several ethical questions arise regarding if individuals with DMC impairment should be allowed to participate and if so, should it be added additional protections in order to minimize the potential risks. (61) The same principle can be applied when talking about children and adolescent participation in clinical research.

ii) Surrogate Consent to research

In cases where informed consent is not possible to be obtained, surrogated consent can be applied. A surrogate consent consists of an individual or health care team that has decisional legal power regarding medical treatment and research, substituting the need for personally informed consent obtention by the subject himself. In research, a proxy decision-maker should only be applied when the individual has proven incapacity to comprehend the implications of the study protocol and provide a substantiated decision.

A surrogate decision-maker can be appointed by the participant himself through verbal power of attorney and should act according to the participant previously expressed desires and best interests, and attention to the jurisdiction that such individual can act. In cases in which no research proxy decision-maker is appointed, the health care agents (health care teams responsible for the subject) have the duty to respect the previously stated patient's wishes in cases they were previously assessed and, through standardized methods, act in accordance to the patients best interests. (49) The American Alzheimer Society states that if the patient is incapable of giving explicit consent, only in cases when the minimal risk is not exceeded may a surrogate consent be applied. (48)

An advance directive, in the medical panorama, is an official document that describes the individual desires and instructions for future medical situations in the scenario where the person is incapable to provide informed consent to a determined health care act. In contrast, the power of attorney asserts that the authorized person has to make decisions for the individual with proven incapacity and such decisions have to be proven and according to the patient's best interest and last previously assessed wishes. (48)

From an ethical perspective, research in volunteers not capable of giving informed consent, the resource to a surrogate decision-maker enters in conflict with the ethical principle of respect for autonomy. In incapable to consent patients, their decision-making autonomy is limited or fully abolished, meaning that their right to auto-determination is conditioned and it is hard to fully respect the previously stated wishes since the background of such decisions may come from an invalid decision making background process determined by their clinical state. Albeit this fact, the principle of beneficence and nonmaleficence have to be respected since the surrogate decision-maker, being an appointed individual by the volunteer or the medical team responsible for its medical decisions, has to respect and act according the participants previously stated wishes and/or its best medical and social interests while diminishing any harm or risk.

It is not often seen patients with specific advance directives for research, but the same criteria applied in general clinical practice should be applied (principle of beneficence) in cases in

which the patients had shown previous interest in participating in a clinical study. In cases where no advance directive has been previously made, the proxy decision-maker (designated through verbal power of attorney) has the power to make a decision regarding participation in research when it is based on the patient's best interest and previously expressed wishes of enrolment. In the cases where there is no advance directive or a proxy decision-maker, the healthcare guardian (e.g. medical team responsible) should decide according to a standard of the personal benefit of the patient when there are no prior wishes assessed. All the previous points have to be made according to the full application of the legal jurisdiction. (52)

The following table (Table V.3.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.3. Illustrative Study Case III	
A study designed to assess the efficacy of a third-generation antipsychotic drug in the treatment of schizophrenia and the cognitive impairments that may result from such pathology. Study population based on individuals diagnosed with CIs associated with schizophrenia resulting in a lack of DMC, through a previously validated scale. Assessment of the symptomatology associated with schizophrenia through programmed interview and CI/DMC through valid scale in periodic appointments.	
Ethical principles	**Respect for Autonomy**
	Beneficence
	Nonmaleficence
	Justice
	Clinical equipoise
Ethical analyses	The principle of justice/equipoise entices that every patient, disregarding their socio-economic backgrounds and their clinical panorama, deserves the best treatment achievable and that research is produced in order to improve such treatment, which in this case represents a moral obligation in representing cognitively impaired patients in research for their diseases. Such research has to be conducted aiming to benefit that population while minimizing harm. The autonomy of the potential participants should always be respected, but for such autonomy to be exerted, he/she needs to have sufficient cognitive capacities to valid and explicit consent to research. The extent of those impairments should be assessed through valid methods (e.g. scales) in order to deduce the following methods that should be applied in order to enrol the patients. Since their cognitive impairments affect their decision-making capacity/process, it is sometimes necessary to resort to a surrogate consent. As stated in the previous text, and according to the international and local jurisdiction, the resource to a surrogate decision making has to be made according to the previous wishes of the potential participant and his/her best interests.
Proposed solutions	• Apply a valid cognitive assessment tool, supported by substantial evidence; • Simplify the process of giving information to potential participants during the inform consent process in order to minimize the effects of the cognitive impairments; • Carefully define the criteria for the resource of a surrogate decision make to archive a surrogate consent.

6. Particular Issues of Randomized Clinical Trials

i) Phase I Trials

Since its design comprehends the participation of voluntary healthy participants, serious ethical issues may arise since there is no direct benefit for those who are enrolled in the trial. Although essential as the first step to a clinical trial, precautions about volunteer's safety have to be deeply scrutinized as well as the assurance that all ethical and legal requisites are compiled. This principle is applicable to all clinical research regarding phase I trials, for the exception of oncology trials (particular design and conduction). (20)

ii) Active comparator

An active comparator translates in a design in which the efficacy of an experimental drug in the experimental group is compared against the results of the standard effective therapy in a control group. The main advantages of the use of an active comparator are the simple fact that every participant will be provided treatment, either via standard therapy or via ED, and the clinical data resulting will already be inserted in the clinical treatment panorama. On the other hand, most of these studies are conducted while only trying to prove that the ED does not have lesser efficacy than the standard therapy, translating in a non-inferiority trial and a "me-too" drug. Those that aim to show significant superiority of the experimental treatment will require an increased number of participants to be exposed to the risks inherent to clinical trials in order to achieve data with sufficient statistical power. (35)

iii) Placebo-Controlled Trials

The placebo is an inert drug without a pharmacologic effect, which constitutes a challenge when designing and conducting placebo-controlled trials. The outcomes resulting from placebo are variable interindividual, and sometimes even within the same individual, in which difference in pathologies, beliefs, amongst other factors, influence such outcomes. The understanding and accounting of the placebo effect and its unpredictability is necessary for the scientific validity and interpretation of the results of such studies. (43)

The design of placebo-controlled trials is a very controversial thematic in the ethical domain, although many times being a requisite to assure the efficacy of experimental drugs. This fact lies on the fact that the comparison of active principals is not deemed enough to fully estimate drug efficacy since it only permits to argue the relative efficacy of an experimental drug in

relation to a well-established (standard) therapy with significant evidence of its effectiveness. On the other hand, the use of a placebo as a control allows the comparison of the efficacy of the experimental drug against the baseline (no treatment). (35)

In other words, these produce data on the "full" efficacy of the ED. In cases where the existing therapy has uncertain effectiveness (varies from patients to patient), no efficacy efference about the experimental drug can be achieved without a placebo arm. Although resourceful, it presents several ethical issues regarding the requirement that a percentage of participants in a trial where a placebo arm exists do not receive treatment, and instead receive a placebo. In the case of PCT, the ethical principles of **justice**, **beneficence** and **non-maleficence** enter in conflict with the social best interest since the participants receiving the placebo are deprived of the best therapy available.

This controversy affects most clinical research areas but is an especially delicate matter in psychiatric research. In the psychiatric domain, the withdrawal of psychiatric medication promotes relapses, and, as such, the appearance of psychotic and depressive symptoms, among others, or augmented risk of suicide/suicide attempts. Also, the long-term effects and consequences of relapses and untreated symptoms are not fully known, augmenting potential risks on a long-term scale.

A study from Ostrow *et al*. aimed to assess the perceived experience of the effects of psychiatric medication discontinuation in patients that had taken them for more than nine months and had, or at least try to, discontinued the medication. Around thirty-six per cent (36%) discontinued the medication over a period superior to six months and another thirty-one per cent did it during the first to the sixth month. Only thirty-three per cent discontinued medication in a period inferior to one month. Even with the medium to long period of medication discontinuation, around fifty-four per cent (54%) presented severe withdrawal symptoms, being the most frequent assessed symptom changes in sleep patterns (80%), difficulty in dealing with own and other emotions (76%), increased anxiety (80%) and depressive humour (70%). Other symptoms of physic indole included fatigue (69%), gastrointestinal problems (47%) and concentration issues (61%). The overall rating attributed by each participant regarding all the perceived experience, on a scale of one to ten, presented an average classification of seven in fifty-four per cent of participants (54%). (56)

The previously presented data show a common tendency to mild to moderate withdrawal symptoms after the discontinuation of psychiatric medication. The symptoms appear to be inversely affected by the time-space of the discontinuations, meaning the longer the timeline, the lesser the symptoms gravity. Although a longer time period of discontinuation may

represent lesser symptoms, they still appear in individuals in which such discontinuation is done over a large period of time up to six months.

The ethical bases on depriving psychiatric participants of the “best treatment”, although deemed necessary to a placebo-controlled trial, is still debated in the psychiatrists’ community, since it may lead to relapses and dangerous behaviours (e.g. suicide), and could imply the reduction in the efficacy of the previously established therapy. In cases of add-on therapies trials, this ethical problem is not raised since all the participants receive the standard therapy.

The use of a placebo arm in research creates disrespect for the ethical requirement of clinical equipoise and constitutes a direct violation of the Declaration of Helsinki. According to the last, no participant, regardless of the group they are inserted, can be deprived of the best treatment or diagnostic method. (53)

A practical example of medication discontinuation is the washout studies design, in which the contemporary medication is discontinued for a defined period of time in order to study the effects of the experimental drugs from the baseline, eliminating the bias that could happen due to the previous drug treatment. Such studies have in consideration the withdrawal period when this phenomenon may affect the research results. In this type of studies, the period of discontinuation and the period where withdrawal symptoms may be perceived, symptoms may (re)appear or be exacerbated, resulting in cumulative potential risk of harm. (53)

Roberts *et al.* conducted an interview-based study within schizophrenic patients were fifteen procedures were rated as harmful, moderately harmful and not harmful. The participants evaluated four procedures as harmful “(e.g. symptom induction)”, five as moderately harmful (e.g. placebo-controlled trials) and six as not harmful. In addition, other factors were evaluated included the willingness to participate in research and that was compared to the previous assessment of the harmfulness evaluation. The results showed, with some exceptions, an inverse proportionality concerning the harm perceived and the willingness to participate, being the procedures deemed most harmful those that showed lower willingness to participate levels. (60)

The two thousand and two clarification of the Declaration of Helsinki comes to resolve, or at least tries to clarify, some lesser clear subjects, being one of them the use of placebo. As translated, the use of a placebo is only considered scientifically valid and ethical when its use is fundamental “for compelling and scientifically sound methodological reasons … to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method.” (54)

There is little to no current guidance regarding the use of placebo in research and clinical practice. In Canada and the United Kingdom there are published guidelines or protocols for

such procedures, while in the United States of America, the American Medical Association published some guidelines and recommendations regarding this topic. The later asserts that although the placebo may be implemented in research and clinical practice, participants/patients need to be informed and consent (sign informed consent). Discussion regarding how the knowledge of the placebo administration may influence their effect is still in debate. (66)

The following table (Table V.4.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.4. Illustrative Study Case IV

A clinical trial for a new antipsychotic drug meant to treat schizophrenic patients with a design that includes a placebo arm (control group).	
Ethical principles	**Beneficence**
	Nonmaleficence
	Justice
	Clinical equipoise
Ethical analyses	The discontinuation of antipsychotic medication has a high potential of causing treatment regression (relapses and symptom worsening). Also, it is deemed unethical depriving participants of the best treatment available. On the other hand, it is not scientifically valid to compare the new treatment only to the best treatment available since it doesn't permit the comparison from a baseline.
Proposed solutions	• The resource to a placebo arm in clinical research should only be made when the evidence produced through a comparison against only the best treatment doesn't produce enough evidence in order to assess the full efficacy of new drug therapy. • The patients in the placebo arm should be closely monitored regarding relapses and/or symptom worsening, and in situations in which such cases are assessed and the investigator determines an augmented risk for the participant, he/she should be removed from the study and given the best treatment available.

iv) Randomization

Randomization can be defined as the process by which, through unbiased randomizer method, participants are allocated to a certain arm group of the RCT. Such a method has to present the same odds of a participant to be allocated to one group as it has to another. Randomization is only considered ethical when there is significant doubt about which is the best treatment when comparing the different study arms. In such cases that there exists one "favourite" treatment in detonation to another, ethical issues may arise. Those ethical issues are only relevant when the beliefs on the superiority of one intervention in relation to another are grounded by systematic evidence, and not only the physician´s particular opinion. (5)

v) Safety and Efficacy Monitoring

The use of an intervention in clinical research comprehends not only the predicted side effects but also an increased risk of such effects or the appearance of unpredicted ones too. These findings are very relevant in order to assess the safety and construct the clinical pharmacological profile of such interventions. In a scientific and ethical manner, the safety outcomes must be closely monitored, with the intervention of all the clinical team, in order to maintain the principles proposed in the design of such study. In terms of efficacy monitoring, the same principles previously referred apply, in such manner that in the conduct of the study the efficacy is continuously assessed. Both monitoring phenomena must occur continuously in every step of the clinical research in order to assure that the risk-benefit ratio and efficacy, previously proposed, is maintained and the efficacy of the intervention is clinically significant individually and when compared to standard therapy or placebo. In cases where the predicted risks are augmented, through several possible reasons, and they outweigh or are not proportional to the benefits, it is unethical to continue the trial. In terms of efficacy, if it is shown low/lower levels of interventional effect, it is also unethical to continue to submit the participants to risks when the benefits are not clinically significant. (20)

7. Special Contemporary Issues

i) *Internet*-based Research

With the internet exponential growth, both in accessibility and features, the use of the internet to partially or totally conduct clinical studies has come into debate regarding to the ethical and functional vulnerabilities it may represent.

The use of the internet as a form of communication in a clinical research setting is typically done to obtain and achieve data according to the individual specifics of the study itself. This data acquisition can occur, given an example, via email or electronic message trading platforms. For example, an observational study consisting of answering questionnaires may be applied through an online base or, by contrast, an interventional study may use the internet to substitute periodic consultations during its conduction and later in the follow-up period.

A systematic review by Hokke et al. analysed fifty-eight (n=58) studies in terms of the use of online methods, exclusively or intercalated with offline methods, to recruit, retain and trace the participants of such studies. The results translated in a proportion of fifty-five per cent (thirty-two studies) using both online and offline methods, and forty-five per cent (twenty-six studies) using online methods exclusively. The most common online methods to have been found were the use of email and/or social media to recruit and communicate with participants along with the study development. (33)

There are several evident benefits in the use of the internet as a mean of communication such as facilitating data acquisition by removing the need (partially or totally) of displacement to the research centre or the easy accessibility to the data by the investigators and other professionals involved. On the other hand, issues regarding the **privacy** of the study's data may arise. The internet represents an exploitable mean to gather information, as often seen in several cases of personal data being leaked to third-party companies or the general public, and the clinical data are no exception. Solutions arise such as the implementation of much stricter protection measures to the clinical research databases providing high-level security to that data. (52)

The following table (Table V.5.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.5. Illustrative Study Case V	
An observational prospective study design aimed to assess the influence of previous depression episodes that required medical attention in the development of schizophrenia through data acquisition via previously registered clinical history (hospital information) and online platform – message board – to assess the symptom severity (through previously defined valid scale) and personal experience. Consent is obtained in person during the psychiatric medical appointment.	
Ethical principles	**Privacy**
Ethical analyses	The use of online services to collect data can create a bias of data acquisition through miscommunication of results and/or different interpretations of the used scale; susceptibility of privacy issues of using an unprotected online service to obtain and retain personal data. The design of the study would be deemed ethical if the privacy and confidentiality of the data would be guaranteed.
Proposed solutions	A careful and simplified explanation of the scale accompanying the same; Creation of a uniformized platform that codifies such data and has very restrained access criteria (e.g. selected IP addresses) in order to reduce the potential leaking of information.

ii) Return of Genomic Results

The return of results in research is a currently debated theme when it comes to the disparity of opinions around the subject, with some researchers arguing that all information regarding the results should be given back to the research participants and others that it would be unethical since the results may cause harm, either physical, psychological or social-economic. (70)

In the recent years, genomic research has been developing a progressively bigger clinical validity in the medical and pharmaceutical care in accordance with the progression of the technologic meant to assess the genomic code with increased precision and possibility of researching new domains. In clinical research, there are often found studies in which the

experimental drug is only effective in individuals with a certain specific gene code or studies that utilize the genomic study to predict or diagnose certain conditions.

The return of results in genomic research represents an unexplored ethical domain with no consensus amongst health professionals, pointing out several advantages alongside with numerous disadvantages coming in the form of possibilities of harm.

An opinion article by Lázaro-Munõz *et al,* in the Journal of Molecular Psychiatry, debates the advantages and opportunities of the return of psychiatric genomic research and compares them with the potentials of causing harm in several domains. Several arguments in favour of the return of results such as the principles of beneficence – potential of improving health outcomes –, respect for autonomy – participants should have the power to decide of whether they want to know their results or not –, justice – participants may not be able to receive their personal genomic information through other means then research (cost related) – and other findings, such as reciprocity, and the fact that most patients want to know their results. On the other hand, the high cost of genomic tests – draining of already scarce research funds –, nonmaleficence – complexity of the genomic information may cause unmeasured emotional stress and psychological harm since participants mays overestimate the risk –, promote therapeutic misconception – participants may associate the return of results with the research being done only to their personal benefit and not an overall gain –, and other arguments, such as difficulties in conduct and return results by lack of physicians training in genomics and the lack of empiric information around different pathogenicity of genetic variants. (64)

The return of results in genomic psychiatric research should be done according to a carefully determined positive benefit-risk ratio, as in any research protocol, and previously determined criteria. In order to be deemed ethical according to the pondered ratio between the potential benefit and the potential harm, the return of results should be done according to the pertinence of the information. In the return of genomic results is of utmost importance to have in mind the psychological sensibility of the psychiatric population. (42)

If the results can indicate a possible diagnose or corroborate the diagnosis of a pre-existing condition they should be shared because the predicted benefits would be greater than the potential harm. Other cases may justify sharing the results, such as cases in which the potential harm is assessed as minimal by the researcher or situations where keeping the results from participants may represent a significant health risk. (64)

It is mandatory that the study protocol and, subsequently, the informed consent predict the return of genomic results, and strictly define the indole of results to be share as well the criteria used to assess the eligibility of such return. The informed consent has to necessarily present all these criteria since it is required the patient's explicit consent. The following table (Table

V.6.) intends to give an example regarding the practical applicability of the discussion presented in this subheading. (61,62)

Table V.6. Illustrative Study Case VI	
A clinical study aimed at assessing the genetic variances of genes deemed of interest in patients suffering from depressive disorders.	
Ethical principles	**Respect for Autonomy**
	Beneficence
	Nonmaleficence
Ethical analyses	The participants have the right, in accordance with the defined criteria in the informed consent, to know their results from research. In accordance with the principle of respect for autonomy, participants have the right to decide if they want to know their personal information resulted from research. But such autonomy should not surpass what is defined in the study protocol and was accepted by the participant while given explicit consent through informed consent. The defined criteria of return of results should be done, besides from what is defined in the study protocol, individual analysis of the case to case. Some patients may benefit from knowing their results, while others may cause harm in the physical, psychological (stress) and social-economic domains. A clinical study aimed at the above example would be deemed ethical only if its protocol would predict the criteria for return of results.
Proposed solutions	The study protocol should: • Define general criteria for return of results (e.g. content); • Permit a case-to-case judgement by the researcher of when what and how should be transmitted to the participants.

8. Other Issues

i) Independent Peer-Review

Conflict of interest is a common possibility when designing and conducting clinical research. Professionals involved in clinical research, especially investigators, according to their professionals' objectives (affiliation with the CRO), or even personal interests, may enter in conflict with producing a clinical study with the social best interest in focus. In order to reduce such bias, the practice of using an independent (no affiliation or professional/personal interest) peer-review is now common practice. Such practice is mandatory in order to respect the ethical principles that rule clinical research and produce scientific and social valid data. (22)

ii) Privacy and Confidentiality

Privacy and confidentiality entice the occlusion of participant data, including personal and clinical, unless the owner of such data explicit consents/permits its exposure. The maintenance of data confidentiality is a mandatory duty of any personal involved in research and it evolves all phases of the study, including publications. Only in very specific circumstances may the confidentiality be broken. Investigators may still have to disclose the research data and specific participant data to funding agencies or national/international monitoring agencies. (55)

In psychiatric research, as seen in psychiatric clinical practice, the resource to family members or relevant nonfamily individuals to collect information is often used to study social interactions and patterns. (52) Such fact creates a space for confidentiality/privacy exploitation, in which should be assured by the physician that any information disclosed will be kept confidential by both parties. It is recommended the use of informed consent in order to guarantee the legal bond of confidentiality.

Regardless of the previously stated factors, the study protocol has to predict and discriminate how the data are collected, who collects and has access to them, and what exceptions may be taken in consideration for the disclosing of such data. The informant has to explicitly address this topic in order to obtain explicit consent from the participant, including the use of the collected data for publication purposes.

Breaches in confidentiality have a bigger impact on medical conditions in which stigma exists since it can provoke psychological and emotional damage to the participant by affecting his personal life. (62) In psychiatric disorders, it becomes even more relevant since such

disclosure may mean that the individuals around the life of the participant may become aware of its mental condition and adversely affect his life in a negative way.

iii) Funding of Clinical Trials

The pharmaceutical industry is the main propeller of research, mainly through funding. The results of funded research are objectively more vulnerable to bias because of the industry's personal interests, especially in data disclosure and publication, than industry independent research (e.g. academic research). Such bias can come as study protocols aimed at the obtention of specific results of interest in deterioration of valid scientific gaining, or publication bias in which the data disclosure is only aimed at positive results instead of full unaltered data disclosure. (35,50) Albeit to the exacerbated risk in funded research, independent research is not safe from such bias. Investigators tend to disclose and publish positive results more often than negative results at the cost of scientific validity for personal gain/interest. (35,50)

iv) Conflicts of Interest

Conflicts of interests are a common theme in research. Funding, as previously stated, represents a major potential of conflicts of interest, both in terms of publication and commercial bias. The personal interests of researchers are normally intrinsic with publication interests, in which, through financial and/or scientific gain, researchers intentionally suppress, modify or delay the results of a study for its own direct or indirect benefit. The commercial bias is understood from the self-interests of the industry itself, normally the one funding it, in producing positive results that will culminate in, for example, a positive authorization for drug commercialization or simply increase their sales through an augmented number of prescriptions, resulted from positive evidence. The coercion of the industry itself to manipulate results, as in individual level, can lead to false data publication. (50)

In order to reduce the effect of such bias, in any publication, it is necessary that the authors and all personally involved state their potential for conflicts of interest and it is of the responsibility of third parties, through methods such as peer review, to assess the effect of such conflict and take action regarding it.

Chapter V

Conclusions

VI. Conclusions

Clinical research has evolved at an exponential rate, accompanying the scientific and technologic progress while being deeply influenced by the evolution of social mentalities and the consequential ethical basis in which those societies are inserted. Both the public and private sector are needed to cooperate in order to accomplish scientific progress. Nonetheless, in order to achieve the best scientific evidence in a clinical research panorama, the basic ethical principles and contemporary social ethics must be respected to their full extent.

Appropriate study design has to be based on valid scientific knowledge and methodologies that translate in new knowledge for the benefit of humankind, but it is also mandatory that every step of the research is ethically sound. Such facts lead to challenges for the sponsors and investigators since they have the duty to ensure that the study's design is based on an appropriated methodology that permits the obtention of meaningful results in order to answer the research question(s), while assuring the best interests and safety of every single participant.

The psychiatric population is a heterogeneous group with diverse demographic and social backgrounds that share one major factor: they constitute a high risk-group, highly vulnerable/susceptible to ethical flaws such as injustices, coercion, exploitations and maleficence in all domains. Most ethical aspects involved in clinical research, scrutinized in the previous chapters, are transcendent to all research but demonstrate an even greater relevance in this population.

Numerous guidances have been published and updated along the years, in an attempt to best protect the participants of clinical research while maintaining the scientific validity of such research and the best social interest. Although the efforts to establish an empiric consensus that allow the design and conduction of clinical research without ethical constraints have come a long way, we are still far from achieving an "ethical utopia".

The clinical psychiatric research setting, even in modern times, stills suffers from medical and social inequality, not only regarding research design and implementation but also in the proportion in which it is made. This fact is brought up by not only the ethical constraints caused by general clinical research, being those clinical trials or other clinical study types, but also the specificity of the psychiatric population. Those "differences" in the population in terms of the mental state create exacerbated hardships in what is deemed ethical to conduct and what is not.

All patients have the right to participate in clinical research and have their diseases being a target to research. Psychiatric patients are often denied participation in clinical trials for their comorbidity nonpsychiatric pathologies and even their participation in the psychiatric focus studies may not be allowed. This not only creates disparities within the psychiatric population on its own but also creates a bias on their representation on the clinical data of pharmacologic data even if they will be a target of the prescription of the approved drugs.

The fundamental topics discussed in this master thesis – research & scientific value; participant selection and recruitment; financial incentives; risk-benefit assessment; informed consent; particular aspects of the clinical trials; special contemporary issues; other issues – demonstrate that starting from the design of a clinical study until its ending, the ethical principles and values have a major role regarding the respect and safety of every single one of its participants but also to assure that its design and conduction are done towards the goal of the best scientific gain for both society and science.

The methods implemented in the design of a clinical study have to present high evidence of their value, but also the favourable outcomes must represent a valid benefit to society and science. Included in those methods are the population selection and individuals' recruitment in such a way that the best interest and safeguard of the participants, regarding their individual and group characteristics, are guaranteed.

A clinical study, whether being interventional or observational, needs to provide a potential benefit for society and science that justifies the proportion of risks participants undergo. Even studies that have a demonstrated minimal risk for patients are not exempt to provide relevant contributions to the scientific knowledge since it often relays on the participation of high-risk individuals. A patient's willingness to participate in research is dependent on the perceived potential harm that can be caused, and, as such, acts in an inversional proportionality. This fact creates a potential inequality of willingness to participate in patients that are unable to comprehend the full extent of the potential harm that can outcome from their participation.

To promote physician enrolment of patients and promote participant adherence to the clinical study, financial compensations are usually protocoled in order to cover all expenses as well to compensate the times and efforts spent. Such compensation should not be high enough to surpass the awareness of the risk-benefit assessment and produce an erratic and risky enrolment/participation.

The informed consent is a mandatory legal and ethical requirement in order to prove the participant willingness to participate in research while having into consideration all the risks, duties and rights that accompany such enrolment. In other words, it is necessary a well-informed agreement to participate. Factors as cognitive impairments or lack of legal capacity

to consent (e.g. children and adolescents) can potentially affect the individual decision-making capacity resulting in the need for additional procedures to validate those participations. Procedures such as the simplification of the study's protocol transmission in order for it to be of easier comprehension can present as a possible solution for the enrolment of cognitively impaired patients in research.

New paradigms and issues are a result of the advances in scientific and technologic knowledge. Given an example, the advances in medical genetics brought countless benefits to the perceptions of fundamental human biology and the pathogenic pathways but also resulted in new ethical issues regarding the privacy of the individual genome and its manipulation to achieve clinical benefit. Other examples include the use of the internet to enrol and monitor participants in clinical research, which may provide new obstacles such as privacy issues.

Funding and conflicts of interests are examples of other issues that can outcome regarding personal and corporative interests. The peer-review constitutes a means to assess the influence of third parties in the design, conduction and publication of results. Every single clinical study has to assure the privacy and confidentiality of the clinical data of all participants.

Clinical research which is meant to obtain clinical data that leads to evidence regarding hypotheses or intervention is highly vulnerable to ethical constraints. The ethical constraints that affect psychiatric clinical research, although having been in the spotlight of major ethical debates, still represent a highly susceptible area that should be analysed case-to-case. The knowledge of such issues combined with the scientific community's efforts may one day culminate in the formulation of an ethical "utopia" where no unjustified harm is caused, and the social and scientific potential outcomes are the main goal.

Chapter VII

Final Remarks

VII. Final Remarks

The following table (Table VII.1) intends to summarize the previous discussion and conclusions in order to provide an easily consultable guide.

Table VII.1. Summary of the discussion and conclusions

Domain	*Subdomain*	*Definition and Content*	*Ethical Principles and Values*		*Scope*
Research Value & Scientific Value	-/-	Research value - a social benefit that can outcome from the research. Scientific value - the attributable value of scientific principles and procedures.	Justice Nonexploitation & Noncoercion		Both ethical criteria translate in the resource to valid scientific principles in order to potentially obtain social benefits since it is only ethical to conduct research when values are respected partly justifying the risks underwent by the participants.
Participant Selection and Recruitment	General	The study's protocol design regarding the selection and recruitment procedures.	Justice	-/-	The study protocol must have a strictly defined population and eligibility criteria (inclusion and exclusion) in order to optimize the clinical study.
	Children and Adolescent Population	A study designed to include, in exclusivity or not, individuals with ages comprehended between 0 to 17 years.		Respect for Autonomy Minimal risk assessed	The inclusion of children and adolescents in research should only be done when no other population within a higher age group (≥ 18 years) able to make a legal/medical decision and can produce the same level evidence regarding the study's results. The resource to include minors in research has to be based on the principle of minimal risk while offering potential benefits both to society/science as well to the individual participant. The consent to participate has to be done by the legal guardian of the minor but the wishes of the minor should always be assessed and respected.

	Geriatric Population	A study designed to include, in exclusivity or not, individuals with ages superior or equal to 65 years.		Respect for Autonomy Nonexploitation & Noncoercion	The inclusion of individuals in geriatric age in research has to be done with regard to the differences and vulnerabilities of this population. Phenomena such as CI that impair the DMC are common in geriatric patients. Assessment tools of the cognitive capacity are needed to assess their capacity for participating in research.
	Imprisoned Population	A study designed to include, in exclusivity or not, individuals that are presently (concerning the study's conduction) imprisoned in a prison facility.		Respect for Autonomy Nonexploitation & Noncoercion	Prisoners are highly susceptible to exploitation due to their social condition. The inclusion of such individuals in research has to ensure that there are no exploitation or coercion forces conditioning their participation and their autonomy is respected.
	Pregnant Women Population	Study designed to include pregnant female individuals .		Nonmaleficence	Clinical research design to include pregnant women has to assure a minimal-risk and high evidence of nonteratogenic effects of the ED.
Financial Incentives	General	Defined protocol for the financial compensations regarding participants time and effort spent.	Justice	Beneficence Nonmaleficence Nonexploitation & Noncoercion	Financial incentives to both investigators and participants should be done through strict procedures in which the monetary compensation only covers the time and effort spent while covering all expenses. In cases where the valour is higher than what is justified to entice the recruitment/participation, it can potentially cause disparities in both phenomena and result in harm.
	Drop-out Rates	Rates by which psychiatric participants drop-out from research.		-/-	The high drop-out rates of psychiatric clinical research provide evidence regarding a major challenge in conducting studies in such population.

Risk/Benefit Ratio Assessment	General	Assessment of the ratio between the risk's participants undergo regarding participation in research and the potential scientific and social gain, and to some extent, individual benefit.	Justice Beneficence Nonmaleficence	The risks that participants undergo resulting from their participation in research has to be assessed as inferior to the potential benefits to society/science. In populations such as cognitive incapables or minors' individuals, those risks have to be deemed minimal and the potential benefits relevant in order to justify its conduction. The positive ratio between the risks and benefits is one key element to justify the conduction of a clinical study.
	Suicide Risk Management	Previously defined a protocol for evaluating and manage suicidal ideation.		Suicidal ideation is a common outcome/symptom of psychiatric disorders. Research protocols need to have established procedures in order to assess such symptomatology and to detail how to act according to the participant best interests.
Informed Consent	General	Legal requisite to prove the informed willingness to participate in research.	Respect for Autonomy Nonexploitation & Noncoercion	The informed consent is the ultimate tool of assessment of willingness to participate in research with the full knowledge of all procedures and potential risks (when done right). In cases where the informed consent is signed although the participant does not fully understand the study and the possible consequences/benefits, it cannot be considered valid or ethical.
	Cognitive Impairments and Decision-making Capacity	Cognitive deficits can potentially result in an incapacity to make decisions regarding one's health (DMC) resulting in a conditioning of the validity of the informed consent in such individuals.		Cognitively impaired patients with demonstrated prejudice to their decision-making capacity. Deficits in one or more DMC domains – understanding, appreciation, reasoning and expression of choice – will be incapable of making an informed decision which translates in an invalid consent to research.

	Surrogate Consent to Research	The resource to a surrogate decision-maker in order to obtain consent for treatment or research in accordance with the established legal criteria.		Patients that cannot consent to research have different alternatives for giving informed consent: • Anticipated directives; • Legal guardian defined by written or verbal power of attorney; • The medical team has decisional power over the individual.
Particular Issues of RCTs	Phase I Trials	Interventional clinical studies performed in a population of healthy volunteers.	Nonmaleficence Nonexploitation & Noncoercion	Healthy participants that volunteer to clinical research need to have particular safeguards regarding their safety and formal compensation for the risks undergone as well the time and effort spent. The principles of nonexploitation & noncoercion are of utmost importance in those volunteers since their participation contributes to the social and scientific gain without any direct benefit to themselves.
	Active comparator	Interventional clinical studies with a control arm subjected to the best treatment available to serve as the baseline for the ED safety and efficacy assessment.	Justice Clinical equipoise	The resource to an active comparator as the intervention given in the control group translating in the best treatment for both groups when the ED is potential, at least, non-inferior.
	Placebo-Controlled Trials	Interventional clinical studies with a control arm subjected to placebo to serve as the baseline for the ED safety and efficacy assessment.	Justice Clinical equipoise Beneficence Nonmaleficence	The resource to placebo as the control intervention represents several risks of causing harm since it translates in the control group not being treated with the best treatment available. In psychiatry, the discontinuation of medication can translate into symptoms worsening/reoccurrence.
	Randomization Process	The process by which the participants are equally distributed between the study's arms.	Justice	The randomization process is often used in order to separate the study's participants through an equally balanced method translating in an equal probability of being allocated to one arm as to the other.

	Safety and Efficacy Monitoring	Procedures design for the best possible assessment (monitoring) of the safety and efficacy of the ED (and study design).	Nonmaleficence	The study's protocol needs to define strategies and methodologies to constantly monitor both the safety and efficacy outcomes.
Special Contemporary Issues	Internet-based Research	Research designed with the inclusion of internet-based resources.	Nonmaleficence Privacy & Confidentiality Result & Publication Bias	Clinical studies that utilize internet procedures in order to conduct research needs to assure the privacy and confidentiality of every personal clinical data. The informed consent obtained through the use of the internet as a mediator as to assure the participant's comprehension of the protocol and subjacent risks. This can be done through a simplified transmission of information (e.g. "infantilization" of the text).
	Return of Genomic Results	Genomic-based research with defined or undefined criteria for the disclosure of genetic results to the participants.	Respect for Autonomy Beneficence Nonmaleficence	For the return of genomic results, it is necessary a case-to-case evaluation of the participant social and medical context in order to determine if such return is beneficial or prejudicial. The information given to the participant regarding the genetic results can be done in totality or only partially. The study's protocol and informed consent have to previously define the criteria and conditions for the return of genomic results.
Other Issues	Independent Peer-Review	Review of the study's protocol by a third-party in order to assure its validity regarding all scientific and ethical domains.	-/-	Independent peer-review is necessary in order to safeguard the scientific integrity of the study's design in both scientific and ethical validity.

	Privacy and Confidentiality	Vulnerabilities regarding personal data privacy and confidentiality.	Nonmaleficence Privacy & Confidentiality	The study's design needs to have defined a strict protocol in order to safeguard all personal data obtained during the conduction of the study (during and after its end).
	Funding for Clinical Research	Public and private funding of clinical research.	Result & Publication Bias Nonexploitation & Noncoercion	Public and private funding of clinical research can represent a window of opportunity for the sponsor to exercise coercion/exploitation forces in order to obtain better outcomes.
	Conflicts of Interest	Influence of personal or corporative interest in the research results.		The personal and corporative interests can outcome in erratic recruitment or any form of publication bias.

Studies

1. Participants and health personal opinions on the conduction of psychiatric clinical research.

2. DMC/CI assessment in the Portuguese psychiatric population.

3. Validation of DMC assessment tools to Portuguese language.

Guidance

1. Psychiatric clinical research ethical guidance.

2. Psychiatric clinical research design, conduction and implementation guidance.

Chapter VIII

References

VIII. References

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