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## Content Highlights

- Biological Psychiatry
- Factorial Trial Design
- Pharmacovigilance
- Translational Research
- Dark Night of the Soul

# Handbook of Clinical Trial Research: Theory & Practice

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EDITOR'S NOTE:

# مکارمِ اخلاق

**Dr. Maryum Azher**
*Editor*

The imagination entwined with the possibilities of biological research has gone haywire. It is not surprising that the modern day action heroes, like Iron Man, Hulk, Spiderman, etc., are all coming from laboratory research experimentations which have not gone as planned. These beings of super natural power set out to take revenge with bad guys and rescue the humanity in the final episode of the Avenger. The evil has also gone online tech savvy. Much of our pre-occupation with biological psychiatry is also the same. The concept half-god, half man (demi-god) which was voiced in Greek mythology has been buried in recent times. We struggle in psychiatry to cope with these evolving paradigms. While drugs seem to numb the pain and relieve the anguish of working through difficult choices which define our work, meaning and purpose in life, the instant relief, sense of entitlement and victimhood festers underneath which is creating a tsunami of mental health issues. Despite advancements in drug development, taking great strides in improving the quality of life and freeing up the people to pursue their dreams, most people are oblivious to what they are supposed to do with their life. Suicide is on the rise, so is depression and other mental health issues.

The gnawing hole or vacuum can only be filled by God. The scientific development and its concomitant corruption with relentless profiteering garnished under the Intellectual property right fuels accumulation of wealth in Capitalism. The essential component of 'service to humanity' has been reduced to lip service. In current times this has raised its ugly head related to the equitable access of vaccine across the Globe. For others to have more, I will have less; somehow we have not reached that level of virtue. The value ethics tells us to embody certain ideals like Truth, Justice, Discernment, etc. and move away from greed, envy, jealousy so that our neighbor doesn't live under the perpetual threat of our individual and collective tyranny. We are told that the life-purpose of Prophet Muhammad was to perfect مکارم اخلاق The root word of makarem is karam, and makarem is the plural of makramah مکرمہ meaning kareem. Kareem, also a name of God or Allah, is very difficult to translate. One can say there is no equivalent word for it in other languages. In general parlance one could say that a man who is 'kareem' is one who is full of virtues. However, keeping the context in mind, we can translate it as noble moral traits, or magnanimous ethics and morals. We lack the lingo to translate the Attributes which are related to the Divine and can be embodied in piece-meal based on actualization of the Selfhood. In the same leg distinction has not been made between the 'Dark Night of the Soul'. It was the John of the Cross (1542-91), a Carmelite priest from Spain, who wrote a poem called the Dark Night of the Soul (Noche Oscura) which describes the spiritual madness which a mystic should endure to be one with his Beloved. We hope you will find the reading worth your time, as we certainly do find it meaningful to collate it under the title of Soul, Newsletter@DUHS. You can send your feedback on the current edition and submissions for the next : **civilitynewsletter@gmail.com**

**Editorial Team**
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# BEWARE OF THE UNEARNED WISDOM

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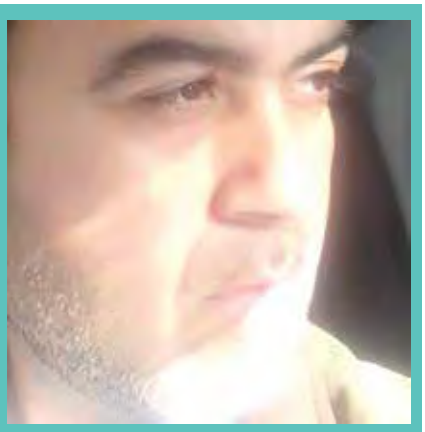

We have entered a new era, post COVID-19, when the familiar structures are crumbling and newer dimensions are gasping for life. The axial shift in civilization is evident for all those who have a nose for research or new things in life. The familiar vistas, theories and methods of science are giving way to an inclusive and holistic concepts. The intuitive perception is supplementing the logical and rational outgrowth of science.

The organic divinity is unfolding to make piece meal, science and practice, come together for the benefit of all. The practice of psychiatry is no different. The biological psychiatry, led by industry, is increasingly scrutinized by the academics and public alike. Psychiatrists are called legalized drug pushers by those who have not benefitted from the incessant prescriptions of psychotropic medications and psychedelics. The non-pharmacological treatment methods and therapies (along with therapists) have also not made any difference. Although stigma related to mental illnesses has been reduced in certain sections of the society and acceptance of going to a therapist has become a norm, a sizable population still languish in emotional, mental and spiritual crisis. You have a gnawing feeling: something has been amiss from the beginning!

Psychiatrists treat what they don't understand (in terms of neurobiology). While they ask about hallucinations (hearing voices) they are oblivious to dimensions of life which is beyond the scope of five senses. It's the fear of going back into the dark ages of 18th Century Europe and descent into the world of superstition. Ironic as it may seem, the baby has been dispensed with the dirty bath water and we are left wondering: what has been all the fuss about!

Psychiatry has been without a soul or inner substance to keep it propped up when subjected to the vigorous examination of its own methods. Well conducted trials fail to demonstrate a clear benefits of the newer medications when compared with the older ones. In fact more patients are dying of adverse events, than the original all-cause mortality with previous generation of drugs. The newer group of medications are developed with clear advantage (at least 10% improvement) and increased tolerability. The Federal Drug Authority (FDA) in United States of America require three large scale Phase III trials for licensing. Generally it takes 10 to 12 years during the early phase trial, incurring a huge cost, before a compound is ready to be tested in human subjects with disease of interest. Naturally, financial motives, and expectation of relief for those who suffer from crippling disease, confounds the robust science. It is only natural to have a bias – an unconscious bent of mind - otherwise who would risk time and energy in investigating newer interventions. This is mostly managed in randomized controlled trials (RCTs). The methodology of RCT ensures that bias is kept at a minimal.

Randomization ensures that factors we know of, and those we are unaware of, like underly-

ing risks, genetic tendencies are distributed equally in both group with no difference at the baseline. Any difference observed at the end of an experiment is due to effect of intervention alone. Of course, the conduct of the trial, allocation concealment, blinding of the clients, investigators and (sometimes) assessors is done so that bias doesn't creep in the RCT. An independent Data Monitoring Committee is charged with the responsibility of foresight to protect the clients against any hazardous effects or stop the trial if a clear difference (statistical or otherwise) is observed between two groups. International Concil for Harmonization (ICH) of Technical Requirements for Pharmaceuticals for Human Use (ICH) is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines (https://www.ich.org). The Guidelines ensure that trial is of high quality, meeting pre-defined ethical and industry standards, so that data generated in one country is acceptable to the licensing authority of other countries who are the signatories.

This edition brings to light the thinking paradigm, methodology, and governance structure which keeps up the biological psychiatry structure propped up. This has stood the test of time, while theories on cognitive behavioral therapy, interpersonal therapy or mindfulness has gained the center stage as a recipe for all aches and pains. A distinction is created that with severe form of illness medications are preferred and for mild to moderate cases various form of psychosocial interventions are effective. However, those working at clinical coal face are well aware that distinction between stages is a matter of time; mild niggles when ignored, can become a


deformity which requires a transplant operation in a joint. Mental health is no different. Dispositions, habits and traits, which are dysfunctional when carried over many years become a liability. Much of the work in managing problems lie in prevention. Public health has recognized that large scale educational programmes, life style changes can reduce the burden of illness. Epidemiology actually calculates attributable risk factors of diseases. If a certain risk factor is reduced by "x" number the overall burden of disease is reduced in 'y' proportion. However, with clear evidence there are fewer who would champion such a cause since there is no money to be made in such interventions.

Physician-pharmaceutical relationship has received attention in recent times; the noble profession of medicine has not remained as such noble. With profit motives ripe, the industry lures physicians from training years. They actually see it as investment which is to be capitalized once a doctor enters the practice. It is not uncommon for sales representatives to voice the notion (which is a fact in certain situations) that we run the educational programmes. It all starts from a small refreshment box at the end of talk to a booking of a venue in a lavish restaurant with all the expenses covered. There is of course the expectation that a pill will be prescribed one way or another. The biological psychiatrisis has gain significance in this regard with most psychiatrist listening only to a point where they have made up their mind on the drug to be prescribed. If listening entails catharsis or ventilation of emotions so that the weary soul can make some sense of his predicament then modern day physicians are deaf.

The spiritual crisis – or dark night of the soul – is something which may require a witness or a counselor who acts as a spiritual director. A sizable majority of people have a problem in living or a life crisis which needs negotiation in terms of doing away with what has finished and preparing for the next stage of life. Life, after all, moves upward or forward in cycles which require negotiating crisis or conflicts. To prescribe psychotropic medications which numb the emotions and make the reality bearable when change should have happened is to delay the inevitable. Pain might be the natural process of living and growing but suffering is an option – by staying stuck to what is familiar and convenient. Lower emotions, like greed, jealousy, deceit, etc. actually work as a firewall baring us from higher insights, wisdom, peace and nirvana. The drugs embody these states albeit temporarily since we all yearn for the lost paradise. Ultimately, the half-life kicks in and we have to wake up to the reality we have constructed. The bad trips with LSD or horror experienced by someone who has been administered mescaline is a reminder that real deal exists which lies on the other side of the horizon of personal responsibility. It was in this context that illustrious Carl G. Jung who voiced that, "Beware of the wisdom that you've not earned!"

A paper on neuropharmacology by Dr Noor Jehan, a novel receptor target for mood disorders by Dr Hani Abidi, animal study by Dr Shafaque Mehboob and a factorial trial design to test pharmacological compound in clinical population by Dr Imran B. Chaudhry exhibits the work done by our peers in the Edition 9, Soul, Newsletter@DUHS.

# HOW RANDOM IS RANDOM

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The finite and mortal humans always had a difficulty comprehending the infinite. Many died & eventually all will die but the riddle of God is still unsolved. Interestingly the cause of the mortality of humans and an inability to comprehend God's wisdom are linked. To appreciate this relationship, one needs to understand the entropic model of aging.

In a closed system, the disorder or randomness always increases. This property of closed systems is known as entropy. While originally described as a thermodynamic property, the role of entropy has been studied in human aging & disease for many years. It is extremely difficult to know the exact cause of deterioration of systems on an atomic level, one plausible explanation could be provided for conscious agents, who use their free will and take decisions after considering relevant factors (input) which ultimately give rise to results (or output). The major determinant of the output is the accuracy. The accuracy of the input data depends upon its quantity as well as quality. The bigger the pool of data & the more accurate it is, the more accurate the output in terms of inference. In simple words, whenever human beings take a decision as conscious agents they considers multiple factors before making an informed choice. When simple in theory, it is impossible to figure out all the variables affecting the outcome; accurately applying it to any situation is easy.

## The major limitations that make the system error-prone are:

- **Infinite causal factors**

  There are an infinite number of variables that could possibly affect the outcome of any event. So no matter how many factors we include in our assessment there will always be factors not accounted for, which will lead to inaccuracies in the output.

- **Wrong variables**

  Another limitation is to include the "wrong" variables as factors which could be a consequence of bias. This leads to corruption of data.

Both of these limitations apply to conscious agents or human error and bias. Therefore left to their own devices they "always" make a wrong choice. They cannot avoid this limitation owing to the finiteness of their ability. This affects the system negatively and it moves towards deterioration. Consider the example of a white blood cell who is encountered with a bacteria. It has two major objectives in order to devise the "perfect plan" to fight the bacteria. One is to identify the exact nature of the bacteria and the second is to deploy the best attack for that specific bacteria. The system would make mistakes at both of these levels would result in damage to the cell itself and sometimes the organisms as a whole. Only through trial and error, the cell learns to fight the bacteria. Every time it undertakes the process it incurs some damage to the system that ultimately leads to its deterioration. In theory, a cell, being a finite intellectual entity, could never consider "all variables" affecting the outcome and therefore could never devise the perfect plan that leaves the system unscathed. Likewise when cells keep making wrong choices they gradually lose their vitality and become old. The fate of all finite agents is to

accumulate the consequences of error and gradually become old and eventually die. This is the entropic basis of aging and disease. By contrast, the only system capable of maintaining its integrity is the one which is able to "consider all factors" & thereby always make the right choice. It avoids entering the deteriorating cycle of entropy.

Such an entity could be equated to something traditionally regarded as God. Based on this discussion we can now define two different types of agents. These can be humans serving agency function.

1. Agents who are able to consider multiple things (but not all things).

2. Agent who are able to consider "all things" (Divinely guided Individuals)

When looking at a single event, the two agents will make different conclusions. The infinite agent that considers all things, would know precisely why he made the decision and would predict the exact sequence of events that will follow in future. Whereas the finite agent, who can consider multiple things but not all, will make different conclusions. His conclusions, as discussed earlier, would be wrong. Being an intellectually finite being, it is impossible to present a comparison of the difference in the viewpoint of the two agents. The best we could do is to compare decision matrix of the two agents; a very knowledgeable agent who is able to consider many factors with an extremely unintelligent agent who doesn't know anything about the subject.

Let's compare a cardiac surgeon to a 4 year old boy who accidentally enters the operation theatre when he's making cuts in the chest of the patient. The boy would probably scream and try to stop the surgeon from doing so and would see the surgeon as a heartless and cruel person. He thinks that he is "killing" the other human on the operating table. On the other hand, the surgeon thinks that he's performing a very noble task by trying to "save" the life of his fellow being. We can safely say that the surgeon is able to consider many more factors, maybe 500-1000 factors, more than the boy that he has learnt over many years of his training. The young child cannot see all those factors and so he protests against it. He even holds negative feelings against the surgeon. One must appreciate that the kid is totally honest when he reacts in this way. There is no external or internal gain for the kid to drive him to protest against the surgeon. He is simply "unable" to see the reality of the event and is genuinely convinced that the surgeon is evil.

In a similar way humans look at God's interventions and are unhappy about it. They are "unable" to see the factors that Divine force has considered. It is important to realize that humans are honest, like that kid, and are making those conclusions because of the finiteness of their intellect. Likewise nobody should look down upon those who don't agree with God but rather the goal should be to enlighten them, make them see more factors so that they can gradually learn to see the wisdom behind God's interventions.

# TESTING THE ROLE OF ADJUNCTIVE TREATMENTS FOR BIPOLAR DEPRESSION

## THROUGH FACTORIAL DESIGN: AN EXAMPLE FROM PAKISTAN

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Factorial design is an extensively used type of clinical trial that allows investigators to examine the effects of two or more compounds or treatments simultaneously. Factorial design offers a more comprehensive approach to investigate treatment outcomes and have advantage over other designs in certain conditions, such as, if investigators are interested to investigate the effects of two treatments, a trial with factorial design may be a more efficient choice as it requires fewer total participants to test each treatment than would be needed to conduct two separate single factor trials.

### Example from Pakistan

A factorial (2x2) randomized controlled trial of minocycline (tetracycline antibiotic) and celecoxib (cyclo-oxygenase-2 (COX-2) inhibitor) added to the treatment as usual for patients diagnosed with bipolar I or II disorder and current major depressive disorder can further help to strengthen the understanding about factorial RCTs. Existing evidence from open label studies support the potential benefit of minocycline for bipolar depression (Murrough et al., 2018; Soczynska et al., 2017). Similarly, evidence from two small clinical trials highlight the promising results of celecoxib in bipolar depression (Edberg et al., 2018; Nery et al., 2008).

The present factorial RCT aimed to investigate the tolerability and efficacy of minocycline or celecoxib added to routine clinical care in adult patients with bipolar disorder experiencing a major depressive episode

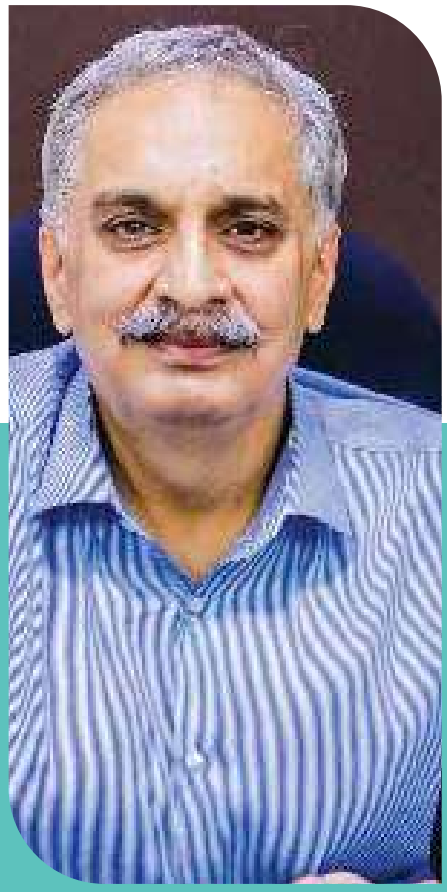
### Study Design:
A four arm, double-blind, placebo controlled, 2x2 factorial trial

### Ethics Approval:
Ethics approval was sought from the institutional review board of Karachi Medical and Dental College in Karachi, Pakistan (IRB- 016/16).

### Trial Registration:
The trial was registered on clinicaltrials.gov, trial registration number NCT02703363

### Study setting:
Karachi, Hyderabad, Lahore and Rawalpindi, Pakistan
Recruitment Centers: Potential participants were approached and recruited from outpatient psychiatry departments.

### Participants:
Patients (n = 226) aged 18 to 65 years, with diagnosis of bipolar I or II disorder and current major depressive disorder with a score of ≥18 on the 17-item Hamilton



Depression Scale, taking their current medication for at least 4 weeks before the baseline assessment, ready to take oral medication in tablet form, willing to use contraception, and female participants willing for monthly pregnancy tests.

Patients with serious physical conditions; history of adverse effects or allergies for any of the anti-inflammatory medication or tetracyclines; currently prescribed with penicillin and or anticoagulant medication; current use of non-steroidal anti-inflammatory drugs, other antibiotics, methotrexate or acetazolamide; high risk of suicide; history of seizures; diagnosis of primary psychotic disorder; a change of psychiatric medication within the preceding 4

weeks; presence of substance misuse or dependence within the last three months; women of reproductive age without adequate contraception, pregnant or lactating women; or those with three or more concurrent manic or hypomanic symptoms were excluded from the trial.

A total of 66-68 participants were recruited in each group (Please see 2x2 factorial design table below).

| | Placebo | Minocycline | Total |
|---|---|---|---|
| Placebo | 66 | 66 | 132 |
| Celecoxib | 66 | 68 | 134 |
| Total | 132 | 134 | 266 |

Randomization: Allocation was determined by the off-site statistician through a restricted, permuted block randomization method. After informed consent and baseline assessment, treatment codes were assigned to the participants by the statistician. Participants were allocated to four treatment arms as per a randomized permuted blocks algorithm after stratification by site to ensure equal numbers in each group.

Masking: The trial team as well as the participants, their carers, and referring psychiatrists were blinded to the allocation details The trial pharmacist had access to the treatment allocation list for un-blinding. The un-blinding which would only proceed if the lead investigator (or his deputy) authorized it.

## Experimental Treatment:

- Study medication (Minocycline Plus matching placebo or Celecoxib plus matching placebo or minocycine and celecoxib) or matching placebo, added to participants' treatment as usual (TAU) throughout the duration of the trial (3 months).
- Minocycline started at a 100 mg/daily, increased after 2 weeks to 200 mg daily

- Celecoxib started at a dose of 200 mg/daily and was increased after 2 weeks to 400 mg/daily.

Treatment as Usual (TAU): All participants received routine care by their clinical team. In Pakistan, routine clinical care for bipolar disorder includes treatment with psychotropic medications (traditional mood stabilizers, antidepressants, antipsychotics, sedatives or hypnotics and anxiolytics) and regular follow-up at outpatient psychiatric unit.

### Assessments:

### Primary outcome measure

(primary outcome is defined as the variable that is the most relevant to answer the research question) The 17-item Hamilton Depression Scale

### Secondary outcome measures

(secondary outcomes are defined as outcomes measured in studies or systematic reviews of treatment effects that are pre-specified in the protocol as being relevant)

- Patient Health Questionnaire (PHQ-9)
- Generalized Anxiety Disorder scale (GAD-7)
- EuroQoL EQ-5D
- Clinical Global Impression score
- Social Functioning Scale (SFS) self-rating in 7 domains
- Global Assessment of Function (GAF)
- Adverse effects monitoring - Adverse effects were monitored through scales specifically designed for celecoxib and minocycline.

### Assessment time points:

Baseline, 12-week post-randomization

### Training and Supervision

All the researchers involved in the trial were trained in Good Clinical Practice (GCP). Senior investigators offered initial training on study procedures and assessment instruments and there were regular refresher training sessions through-out the trial. Inter-rater reliability sessions were organized and chaired by the senior investigators.

### Trial Monitoring Committee - Trial Steering Committee (TSC)

The TSC is an independent committee and its role is to provide advice, through its Chair, to the Principal Investigator, the Project Sponsor, the Project Funder, the Host Institution and the Contractor on all appropriate aspects of the project. This includes progress of the project, adherence to the protocol, patient safety (where appropriate) and the consideration of new information of relevance to the research question, the rights, safety and well-being of the participants.

TSC also ensures that appropriate ethical and other approvals are obtained in line with the project plan, to agree proposals for substantial protocol amendments and provide advice to the sponsor and funder regarding approvals of such amendments, and to provide advice to the investigators on all aspects of the project

The TSC for this trial included a senior physician and a service user. The TSC also had the responsibility for data monitoring.

### Results:

- This trial is the largest randomized controlled trial investigating anti-inflammatory agents in adults with bipolar disorder.
- Factorial design makes this trial the first study to concurrently assess the efficacy of minocycline and celecoxib as adjunctive treatments for bipolar depression.
- Neither minocycline nor celecoxib, was associated with an antidepressant effect compared with placebo in the treatment of bipolar depression.
- A putative limitation of this study is that this trial was powered on the assumption that there were no interactions between celecoxib and minocycline. Factorial design studies can often have unanticipated interactions between treatments.

  There was no evidence of any interaction between two treatments in this trial an adequately powered study might find an interaction of clinical significance.

### Note:

For detailed description of methodology and trial findings please see (Husain et al., 2020)

Acknowledgement: Stanley Medical Research Institute

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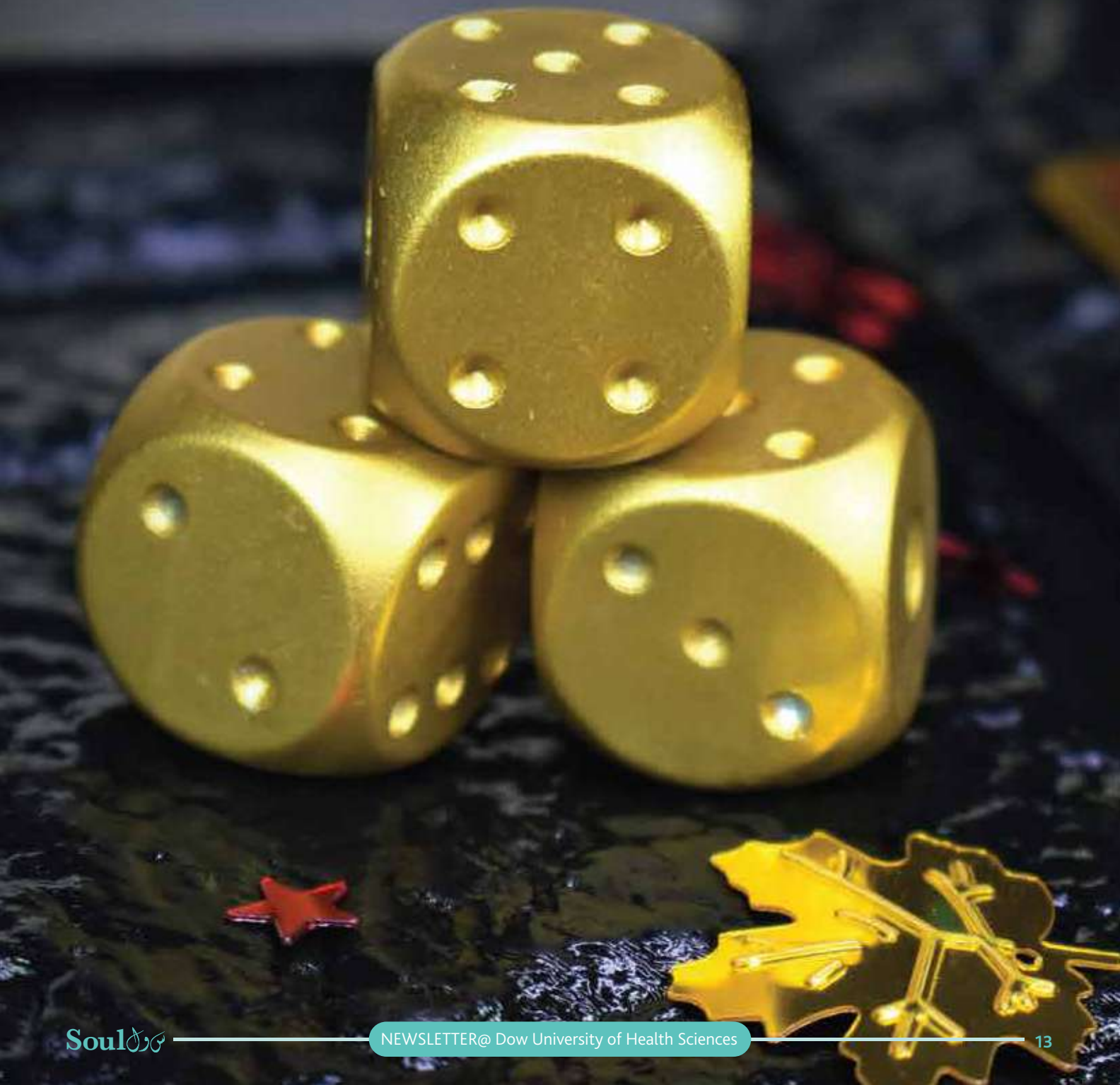

# NEUROTRANSMISSION, MENTAL FUNCTIONS AND ADDICTION: CURRENT TREATMENT AND FUTURE PROSPECTS

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Brain and the nervous system plays very important role in regulating functions of human body. Brain activity is made possible by the interconnections of neurons that are linked together to reach their targets. The chemical neurotransmitter releases at a synapse that propagates a signal that acts on the target cell. These chemical neurotransmitters include dopamine, serotonin, GABA, glutamate, and acetylcholine. GABA is the major inhibitory neurotransmitter in the brain, and glutamate is the major excitatory neurotransmitter.

The brain is responsible for cognition, which functions through numerous processes and executive functions. Executive functions include the ability to filter information and tune out irrelevant stimuli with attentional control and cognitive inhibition, the ability to process and manipulate information held in working memory, the ability to think about multiple concepts simultaneously and switch tasks with cognitive flexibility, the ability to inhibit impulses and prepotent responses with inhibitory control, and the ability to determine the relevance of information or appropriateness of an action. Higher order executive functions require the simultaneous use of multiple basic executive functions, and include planning, prospection and fluid intelligence (i.e., reasoning and problem solving).

Neurodegenerative diseases result in progressive damage to different parts of the brain's function, and worsen with age. Common examples include dementia such as Alzheimer's disease, alcoholic dementia or vascular dementia; Parkinson's disease; and other rarer infectious, genetic, or metabolic causes such as Huntington's disease, motor neuron diseases, HIV dementia, syphilis-related dementia and Wilson's disease. Neurodegenerative diseases can affect different parts of the brain, and can affect movement, memory, and cognition.

Epileptic seizures are thought to relate to abnormal electrical activity. Seizure activity can manifest as absence of consciousness, focal effects such as limb movement or impediments of speech, or be generalized in nature. Status epilepticus refers to a seizure or series of seizures that have not terminated within 5 minutes. Seizures have a large number of causes, however many seizures occur without a definitive cause being found. In a person with epilepsy, risk factors for further seizures may include sleeplessness, drug and alcohol intake, and stress.

Mental disorders, such as depression, schizophrenia, bipolar disorder, posttraumatic stress disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, Tourette syndrome, and addiction, are known to relate to the functioning of the brain.

In addiction is body requires stimulation of reward centers while at the end there are adverse effects of these addictive agents. Virtually all drugs causing drug addiction increase the dopamine release in the mesolimbic pathway, in addition to their specific effects. These are called psychoactive drugs and are urged to administer repeatedly. The reward pathway, known as the mesolimbic pathway, or its extension, the mesocorticolimbic pathway, is characterized by the interaction of several areas of the brain. Dopamine is the primary neurotransmitter of the reward system in the brain. It plays a role in regulating movement, emotion, cognition, motivation, and feelings of pleasure. Natural rewards, like eating, as well as recreational drug use cause a release of dopamine, and are associated with the reinforcing nature of

these stimuli.

Drug seeking behavior is induced by glutamatergic projections from the prefrontal cortex to the nucleus accumbens. drug seeking behavior can be prevented following the inhibition of AMPA glutamate receptors and glutamate release in the nucleus accumbens.

Examples of drug and behavioral addictions include alcoholism, marijuana addiction, amphetamine addiction, cocaine addiction, nicotine addiction, opioid addiction, food addiction, chocolate addiction, video game addiction, gambling addiction, and sexual addiction. Addiction has bad effects on individuals as well as society. There are certain risk factors involved in


addiction as genetic and environmental risk factors.

The environmental factors include stress, poverty, availability of substance and parent's negligence. Transcription factor is a protein that binds to DNA and regulates gene expression by promoting or suppressing transcription. The most important transcription factors that produce these alterations are ΔFosB, cAMP response element binding protein (CREB), and nuclear factor kappa B (NF-κB). ΔFosB is the most significant biomolecular mechanism in addiction because the overexpression of ΔFosB in the D1-type medium spiny neurons in the nucleus accumbens is necessary and sufficient for many of the neural adaptations and behavioral effects (e.g., expression-dependent increases in drug self-administration and reward sensitization) seen in drug addiction.

Withdrawal refers to physical and psychological symptoms experienced when reducing or discontinuing a substance that the body has become dependent on. Symptoms of withdrawal generally include but are not limited to body aches, anxiety, irritability, intense cravings for the substance, nausea, hallucinations, headaches, cold sweats, tremors, and seizures.

All pharmacological or biologically based treatments for addiction need to be integrated into other established forms of addiction rehabilitation, such as cognitive behavioral therapy, individual and group psychotherapy, behavior modification strategies, twelve-step programs, and medication-assisted treatment (e.g., methadone, naltrexone, burprenorphine) in a long-term rehabilitation setting, through a twenty month long ethnographic fieldwork investigation.

Pharmacological treatments for alcohol addiction include drugs like naltrexone (opioid antagonist), disulfiram, acamprosate, and topiramate. These drugs reduce craving of alcohol by producing unpleasant effects when alcohol is consumed, as with disulfiram. Opioid antagonist naltrexone has been shown to be an effective treatment for alcoholism, with the effects lasting three to twelve months after the end of treatment.

Development of CB1 receptor agonists that have reduced interaction with β-arrestin 2 signaling might be therapeutically useful in cannabinoid addiction. Another area in which drug

treatment has been widely used is in the treatment of nicotine addiction, which usually involves the use of nicotine replacement therapy, nicotinic receptor antagonists, or nicotinic receptor partial agonists. Examples of drugs that act on nicotinic receptors and have been used for treating nicotine addiction include antagonists like bupropion and the partial agonist varenicline Opioids (such as dihydrocodeine, dihydroetorphine and even heroin) cause physical dependence, and treatment typically addresses both dependence and addiction. Physical dependence is treated using replacement drugs such as suboxone or subutex (both containing the active ingredients buprenorphine) and methadone. Once a prescribed dosage is stabilized, treatment enters maintenance or tapering phases. Baclofen has led to successful reductions of cravings for stimulants, alcohol, and opioids, and also alleviates alcohol withdrawal syndrome. TAAR1-selective agonists have significant therapeutic potential as a treatment for psychostimulant addictions.

Research indicates that vaccines which utilize anti-drug monoclonal antibodies can mitigate drug-induced positive reinforcement by preventing the drug from moving across the blood–brain barrier; however, current vaccine-based therapies are only effective in a relatively small subset of individuals. The idea is that the body will respond to the vaccine by quickly producing antibodies to prevent the opioids from accessing the brain. Vaccine-based therapies are being tested in human clinical trials as a treatment for addiction and preventive measure against drug overdoses involving nicotine, cocaine, and methamphetamine. Since addiction involves abnormalities in glutamate and GABAergic neurotransmission, receptors associated with these neurotransmitters (e.g., AMPA receptors, NMDA receptors, and GABAB receptors) are potential therapeutic targets for addictions. N-acetylcysteine, which affects metabotropic glutamate receptors and NMDA receptors, has shown some benefit in preclinical and clinical studies involving addictions to cocaine, heroin, and cannabinoids.

Current medical reviews of research involving lab animals have identified a drug class – class I histone deacetylase inhibitors that indirectly inhibits the function and further increases in the expression of accumbal ΔFosB by inducing G9a expression in the nucleus accumbens after prolonged use. Oral administration or intraperitoneal administration of the sodium salt of butyric acid or other class I HDAC inhibitors for an extended period indicate that these drugs have efficacy in reducing addictive behavior in lab animals.

Gene therapy for addiction is an active area of research. One line of gene therapy research involves the use of viral vectors to increase the expression of dopamine D2 receptor proteins in the brain.

# MOLECULAR DRUG TARGETS
## FOR DEPRESSIVE DISORDERS

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### Background

"A mental disorder is a syndrome characterized by clinically significant disturbance in an individual's cognition, emotion regulation, or behavior that reflects a dysfunction in the psychological, biological or developmental processes underlying mental functioning (1)." There is significant distress in social, occupational, or other activities in patients suffering from mental disorders (2). An expectable or culturally acceptable response to a common stressor or loss, such as the death of a family member cannot be classified as a mental disorder. Furthermore, any socially deviant behavior which can be religious, sexual, or political, and any conflict between individual and society cannot be diagnosed as a mental disorder, unless the deviation or conflict results from a dysfunction in the patient as described above (1).

Depression is a mood disorder, as defined by the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5), that combines several symptoms that alter the functionality of an individual (1). Depression disturbs the emotions, cognition, and behavior of patients suffering from it (1). In summary, the diagnostic criteria for a major depressive disorder (MDD) according to the DSM-5, consist of, "a primary symptom – either a diminished/ irritable mood or decreased interest/ pleasure (anhedonia) – or both, and at least four of the following symptoms: feelings of guilt or worthlessness, fatigue or loss of energy, concentration problems, suicidal thoughts or thoughts about death, weight loss or weight gain (5% change in weight), psychomotor retardation or activation (change in activity), hypersomnia or insomnia (change in sleep) lasting for at least 2 weeks (1)." The description of depression can be of a first episode, a recurrent or chronic episode; it could also be termed as mild, moderate, or severe and maybe with or without psychotic features (1).

### Types of depressive disorders

There are several types of depressive disorders also mentioned in the DSM-5 which include disruptive mood dysregulation disorder, major depressive disorder (including major depressive episode), persistent depressive disorder (dysthymia), premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder and unspecified depressive disorder (1).

When one considers the overall impact of depression, some statistics indicate its importance as a significant problem on a global scale. More than 300 million people in the world are estimated to suffer from depression, which is listed as the single largest factor contributing to global disability by the World Health Organization (WHO) (3). The total number of incident cases of MDD increased from 162 million in 1990 to 241 million in 2017 worldwide, indicating an increase of 49.29% (4).

There is one study by Stegenga et al, that followed depressed patients for 6, 12, and 39 months in a primary care setting (5). The majority of participants who were diagnosed with MDD at baseline had an intermittent or chronic course of disease; as much as 57% of patients diagnosed with MDD at baseline had not recovered after 39 months. Their findings are in accord with several community-based studies with follow-up durations ranging from 2 to 49 years in adults diagnosed with MDD which show that about 20% of patients developed a chronic course and about 30–50% had a recurrent course (6-11). The above findings by Stegenga et al suggest that the natural history of depression in primary care resembles that of depression in the general adult population (5).

### Treatment-resistant depression

What is currently relevant to psychiatry in terms of MDD is treatment-resistant depression (TRD). Treatment-resistant depression is another term used to describe persistent depression. The term Treatment-Resistant Depression (TRD) represents what was previously labeled as dysthymia and chronic major depression, according to the DSM-5 (fifth edition; APA, 2013) (12). The patient must present a depressed mood for a minimum of 2 years as indicated in the manual. The mood can be also irritable or depressed for at least 1 year, in the case of children or adolescents. Also, two of the following symptoms are included: (1) Poor appetite or overeating; (2) Insomnia or hypersomnia; (3) Low energy/fatigue; (4) Low self-esteem; (5) Poor concentration/decision making; (6) Hopelessness. Therefore, the broad category of treatment-resistant depression can have an overlap between double depression (dysthymia and major depression) or just chronic major depression. Additionally, it is well documented that up to 30% of patients with MDD are refractory to currently used antidepressants (13).

Despite recent innovations in treatment options, TRD is frequently encountered in daily psychiatric practice and remains an unresolved problem (14, 15). The need for new treatment options in this area is highlighted by issues such as high health care costs (16-19) and suicide rates (20, 21). Owing to an extremely high risk of suicide, TRD can be considered a life-threatening disease. There are reports that at least once in their lifetime, nearly 30% of patients with TRD attempt suicide (22, 23). Compared with non-resistant depression this rate is reported to be at least twice the lifetime suicide rates (24, 25). Therefore, there is a need to explore new avenues of therapy in the management of treatment-resistant depression.

## Molecular drug targtes

Standard treatment options rely on increasing the levels of monoamine neurotransmitters in the brain. The monoamines, namely serotonin, norepinephrine, and dopamine—are all produced in small nuclei in the brain stem (26). Serotonergic nuclei are concentrated in the caudal brain stem while the noradrenergic nuclei are found in the nucleus, locus coeruleus. Dopamine is synthesized in more rostral nuclei, the substantia nigra, and ventral tegmental area of the midbrain. While the monoaminergic nuclei project far and wide throughout the brain, the serotonergic and noradrenergic axons also descend into the spinal cord. This allows monoaminergic neurons to produce synchronized responses and thus to influence functions such as arousal, attention, vigilance, motivation, and other cognitive and emotional states that involve multiple brain regions (26).

When released in response to an action potential, these neurotransmitters either bind postsynaptic receptors or are cleared by presynaptic transporters. Both serotonin (5-HT or 5-hydroxytryptamine) and norepinephrine each have a range of different receptors on the presynaptic terminals as well as postsynaptic target cells. At least 14 distinct serotonin receptors are found in humans, branching from seven major classes denoted 5-HT1

through 5-HT7. Norepinephrine receptors can be divided into two major classes, the α, and β adrenergic receptors, with multiple subtypes. Serotonin, norepinephrine, and dopamine act on G protein-coupled receptors, that initiate signaling cascades that produce long-term changes in the response properties of the postsynaptic neuron. The only exception to this is the 5HT3 receptor. By directly or indirectly influencing G protein-coupled receptors expressed in large numbers of neurons, it is believed that antidepressant drugs can alter the responsiveness of the brain to diverse cognitive and emotional stimuli (26).

Newer generation antidepressants are multimodal and as the name suggests, they work through a combination of two or more different mechanisms (27, 28). In the review by McCormack, the new drug, vilazodone induces the inhibition of serotonin reuptake by its binding to the serotonin transporter, as well as being engaged in the partial agonist of the 5HT1A receptor, theoretically giving it a potential advantage in patients with comorbid depression and anxiety. Vortioxetine, while having reuptake inhibition of serotonin, also has direct actions on several serotonin receptors, which involves antagonism of 5HT1D, 5HT3, and 5HT7, agonism of 5HT1A, and partial

5HT2AR

5HT1AR

agonism of 5HT1B receptors (29). The distinct effect of vortioxetine relating to an improvement in cognition is likely to be linked with its antagonism of 5HT7 receptors.

Recently, ketamine has been repurposed as an antidepressant being known mainly as a dissociative anesthetic. While the precise mechanism through which it acts is not known, it appears to primarily involve antagonism of the NMDA glutamatergic ionotropic receptors, with an increase in numbers of alfa-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors and, ultimately, raising production of brain-derived neurotrophic factor (BDNF) (30). To aid in the treatment of MDD, an intranasal form of esketamine, an S-enantiomer of ketamine, received the approval of the FDA in the year 2019. Where esketamine has a greater affinity for NMDA receptors than ketamine, its efficacy has been demonstrated in the rapid amelioration in symptoms of depression; long-term data is not yet available in terms of effectiveness and safety (31, 32).

The repurposing of ketamine has led to investigations into other NMDA antagonists while inspiring work into the use of drugs that affect the opioid system, the GABA-ergic system, the cholinergic system, the melatonergic system, the hypothalamic-pituitary-adrenal (HPA) axis, the immune/inflammatory system as well as neurotrophic agents and psychedelic drugs (33).

Additionally, there are options used in the management of TRD, like atypical antipsychotics such as olanzapine that works in MDD by blocking the 5HT2A receptor, and aripiprazole that acts as an agonist at the 5HT1A receptor (34, 35). Furthermore, there is the possibility of using deep brain stimulation in severe and refractory cases which comes with the price of being an invasive procedure. In short, the issue of TRD hasn't been resolved satisfactorily so far and this is being addressed in new and inventive ways.

As noted earlier, TRD represents a considerable percent of MDD patients and has significant morbidity and mortality (higher suicide rates), there is a move in literature to publish on alternative treatment options. Herbs are gaining ground as an effective and safe treatment option in MDD (36-40) with earlier onset of therapeutic response and reliable clinical efficacy. Since herbs are multimodal and MDD has roots in inflammatory processes and metabolic disorders, herbs have anti-inflammatory and anti-diabetic actions in addition to the restoration of serotonin balance in the brain, which represent a holistic medical approach towards the treatment of MDD. Thus, literature is currently showing a rise in publications on natural products, and this should be welcomed and received with enthusiasm by the psychiatric community.

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# EVIDENCE TO PRACTICE:
## NEED FOR IMPLEMENTATION RESEARCH AGENDA

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Mrs. M was a young married woman living in a village in rural India. Her husband owned a small piece of land and large amount of debt incurred over last few years due to successive crop failures and borrowing from a private moneylender. This financial crisis was compounded by severe drinking problem, and he often used to beat Mrs. M during the intoxicated state. Mrs. M was looking after her two daughters and few months ago she was pregnant for the third time. The situation was quite overwhelming for Mrs. M. She became very reclusive, looked sad most of the times, got irritable on slightest provocation, and completely lost hope of anything good happening in the future. On multiple occasions, she felt that it is good to 'sleep forever'. Unfortunately, one night she consumed the pesticide kept at home to never wake up again leaving behind two young grieving daughters.

Mrs. M probably suffered from antenatal depression which went completely unnoticed, and she didn't receive any support which led to her suicide. The death of Mrs. M is result of an interplay of very complex social and economic factors, nevertheless her depression, one of the most common mental health conditions cannot be completely delinked from her suicide. It is quite likely that a timely detection of depression and provision of an evidence-based intervention might have potentially saved a life. It is in this context that we seriously need to ask a question, 'Why this did not happen?'

Probably the decision makers and the public health system do not consider depression (and other mental health conditions) as serious public health issues, or they think that we do not have any interventions to address the same or is it simply our collective failure to translate 'what we know' into 'what changes the lives' of people in real world.

Mental health conditions significantly impact all aspects of life and have serious physical, social and economic consequences. They significantly contribute to burden to disease globally as well as in South Asia; they affect individuals across life-course, more specifically those who have social vulnerabilities, reduce life expectancy and the quality of life, result in stigma and discrimination, even human rights violation in extreme cases, impact economic productivity of the individual, the caregiver and the society in general, ultimately leading to huge suffering and unmet needs in the population.

Improving access to evidence-based mental health services is the only way-forward to address this huge burden of mental health conditions in South Asia. Translating evidence into practice is easier said than done. There is a famous 'Iron Law of Evaluation' proposed by Peter Rossi. According to this rather pessimistic law, the average of net impact assessments of a large set of social programs will crawl asymptomatically toward zero. Unfortunately, the interventions that work in initial studies lose their effectiveness as they are implemented widely.[1,2] Clinical and community mental health care provision guidelines are based on the systematic reviews and synthesis of evidence generated from the randomized controlled trials. Quite often, the interventions delivered in these trials are applicable only to a small number of settings. The full range of complexity of the intervention may not be fully understood and this may lead to failure in replication of the results in at least 50% of the replication sites, implying an equal chance that it will or will not work. Many a times, it is not the intervention, which is inherently flawed, rather it is the unpredictable behavior of the health system in which this intervention is attempted to be embedded.[3] Health systems, especially in the low resource setting, lack the capacity to integrate the evidence-based intervention, and within such unmapped and misunderstood systems, interventions, even the very simplest, often fail to achieve their goals. Many a times, interventions that work in small scale pilot studies fail to live up to expectations in national roll-out or fail to transfer from one country to another because of contextual differences.[4]

A number of randomized controlled trials in Pakistan and India have demonstrated that psychosocial interventions developed in the high income countries can be contextually adapted and

effectively delivered by Non-Physician Health Workers (NPHWs) for various disorders[5–7] The major challenge is to translate this knowledge into action. The findings of some implementation research projects in India are particularly encouraging as they demonstrate that mental health services can be integrated and scaled up within a public health system context in a very low-resource setting[8] and that the demand and access to mental health services can be increased at the community level if the work is led by grass-roots community health workers.[9]

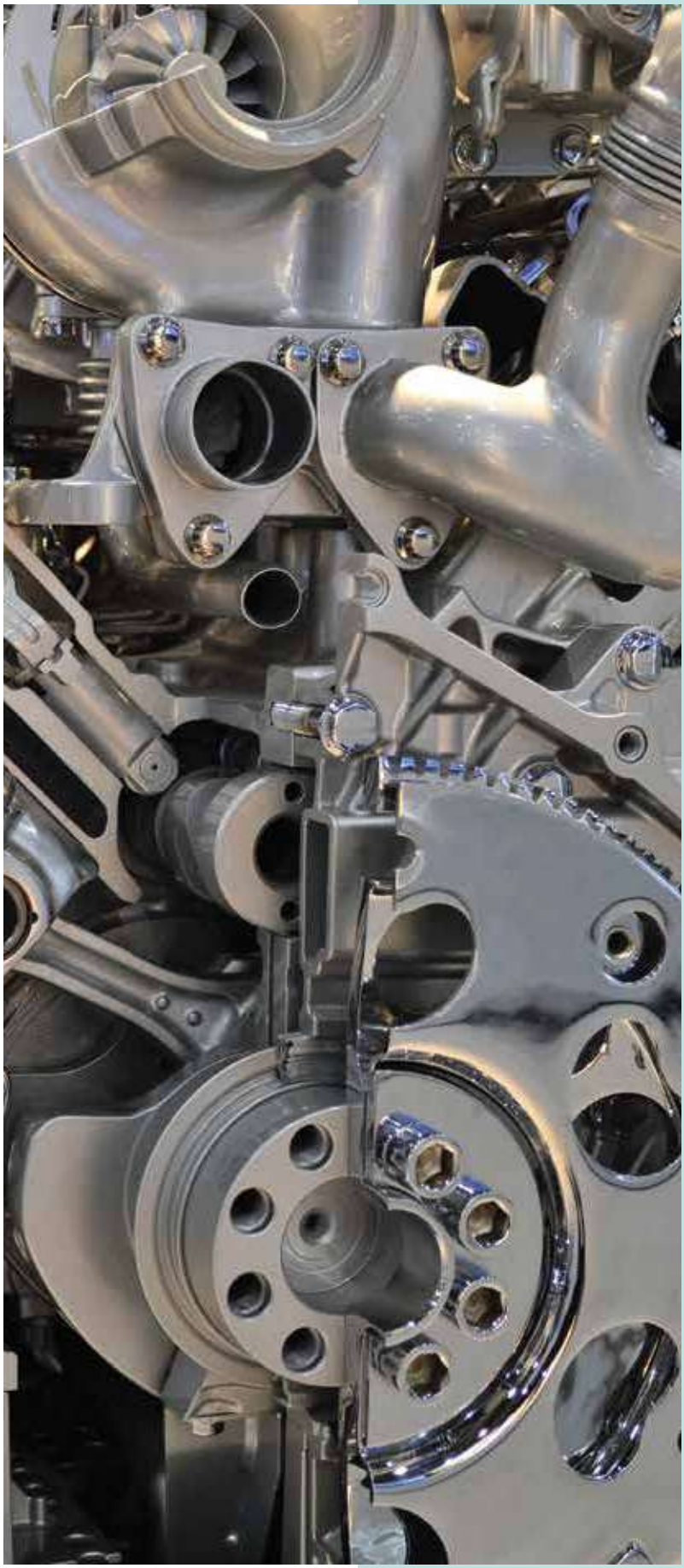
robust implementation research and successful health systems strengthening.[10]

Along with providing treatment to individuals with mental health conditions, it is equally important to improve mental health and the overall well-being of the entire population. India has a rich tradition of Yoga, Vipassana (mindfulness) and other culturally rooted interventions which have been shown to be effective in mental health promotion.[11] Whilst their therapeutic effectiveness still needs to be firmly established, they can

Moving forward, academic (and political) leadership in South Asia should seriously think of prioritizing the implementation research agenda to address this important knowledge to practice gap. Decision makers in the global North (i.e., high-income country institutions) drive the global health research agenda and decide that needs to be investigated and the methods and approaches to do the same. Most of the times short-term research programs with measurable impact are funded. However, a more resource intensive and long-term investment is essential to genuinely engage with community stakeholders and adopters of the evidence-based practice for

certainly be considered to improve the emotional and psychological resilience of the communities which can be helpful in mitigating distress before it deteriorates into a mental health condition.

It is now time for us to get our act together. We should explicitly recognize the need to translate evidence into practice, allocate more resources and fund, researchers and practitioners to scale-up evidence-based interventions and prioritize the overall well-being of our populations.



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# CONTROLLED DRUGS IN HOSPITAL SETTINGS

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Medication storage is an important component of patient safety and it's always a daunting task because of multiple reasons. Medication Storage is not only linked with maintenance of quality, stability but also includes the legitimate use of specified categories of drugs (Narcotics, psychotropic, restricted antibiotics etc.) to reduce the irrational use and theft of medications from hospital premises. There must be suitable facilities to enable the storage and preparation of medications under proper conditions of sanitation, temperature, light, moisture, ventilation, segregation, and security to ensure medication integrity and personnel safety throughout the hospital. For that reason, it's considered as the important element of medication management and use. If not done properly it may lead to medication errors.

Control substances by virtue of their nature are prone to be misused that's why Narcotics are included as high-alert medications by different international bodies like ISMP, ASHP, JCIA, WHO because it bears a heightened risk of causing significant patient harm. Health Canada has published a report regarding theft and misuse of controlled drugs in pharmacies and hospitals and it showed the huge percentage of theft were related to opioid's doses. Data 2014, to 2018, were obtained from Health Canada's Office of Controlled Substances (OCS). Reports of incidents are provided by pharmacies and hospitals. During the studied period, 45,379 submissions to the OCS provided information to create 213,895 entries to the database. After exclusions, 212,317 reports were retained for analysis. Approximately, 29 million individual doses were lost or stolen of which 7.7 million were opioids (26%)

If we discuss the drug use in Pakistan, approximately six per cent of the population, or 6.7 million people had used any controlled substance including misuse of prescription drugs, in the last year and approximately 1.5 per cent of the population, or nearly 1.6 million people, reported nonmedical use of prescription opioids (painkillers) in the past year.

As per the Drug Act 1976 of Pakistan, Strict regulation /monitoring are required for controlled drugs for their storage, prescribing, dispensing, administration, wastage and return to avoid the misuse and theft from the appropriate areas. Any discussion on narcotics, or other controlled substances is usually peppered with the word schedule. Globally these International Drug classifications are to delineate a substance's legality, based on "the drug's acceptable medical use and the drug's abuse or dependency potential". There are total of five schedules internationally.

**Schedule I:** Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Example: Heroin, Marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy)

**Schedule II:** Schedule II drugs, substances, or chemicals are defined as drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence. Example: cocaine, methamphetamine, methadone, Morphine, oxycodone , fentanyl, and Ritalin

**Schedule III:** Schedule III drugs, substances, or chemicals are defined as drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs but more than Schedule IV. Example: ketamine, anabolic steroids

**Schedule IV:** Schedule IV drugs, substances, or chemicals are defined as drugs with a low potential for abuse and low risk of dependence. Example: Alprazolam, Diazepam, Lorazepam, Temazepam, Tramadol

**Schedule V:** Schedule V drugs, substances, or chemicals are defined as drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of

certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes.

## Why safe keeping of narcotics is necessary??

Narcotics are potentially dangerous and addictive drugs for that reason safe keeping and preventing unauthorized access from medical staff and patients are necessary. All narcotics should be stored in lock and key cabinet and keys should be accessible to authorize persons only keeping in a safe place. The cabinet should be made of metal and fixed to the wall or floor. A designated person at the practice should be nominated.

All controlled drugs in schedules II, III, and IV of the controlled substances act are to be stored in the medication cart in separate drawers designated for that purpose. Schedule II controlled substances are to be stored in a locked drawer.

## Responsibility of pharmacist in Hospital pharmacy:

- Pharmacist shall be responsible for the safe keeping of Narcotics.
- Pharmacist shall keep the drawer locked and retain the key with him / her.
- All Narcotics controlled drugs are to be counted at the end of each shift.
- Narcotic medications should be reconciled during shift change
- If the count is incorrect and cannot be reconciled, the pharmacist must investigate.

## Responsibility of nurse at nursing units:

- Narcotic drugs to be stored with two separate keys.
- Each narcotic key should be kept separately under the custody of two registered nurse.
- Assigned registered nurse will ensure that narcotic keys remain in the unit all the times.
- If the nurse goes on break or leaves the unit, she/he will hand over the keys to designated nurse
- After administration there must be second witness.

## Responsibility of Physician:

- Physician must be authorized to prescribe the control medication. Every physician is not allowed to prescribe controlled medications (Narcotics/ schedule II Drugs)
- Physicians must ensure appropriate monitoring to identify emerging risks or complications arising from the prescribed drugs.
- Proper documentation of prescription will be required (no verbal orders can be given for narcotics / schedule II drugs).

## Disposal:

- Medication administration nurse along with witness must ensure to empty all unused narcotics from syringe/ ampoule in danger box & then dispose the syringe in it while the empty ampoules after usage must be returned to Pharmacy along with Narcotic administration record.

### Challenges and Recommendations to overcome them

| Class of drug | Examples of classes | Indications |
|---|---|---|
| Antipsychotic | Phenothiazines | Acute treatment of schizophrenia and mania<br>Prophylaxis of schizophrenia |
| | Butyrophenones<br>Substituted benzamides | |
| Antidepressant | Tricyclic antidepressants | Major depression (acute treatment and prophylaxis), anxiety disorders, obsessive–compulsive disorder |
| | MAOIs<br>SSRIs | |
| Mood stabilizer | Lithium<br>Carbamazepine | Acute treatment of mania<br>Prophylaxis of recurrent mood disorder |
| Anxiolytic | Benzodiazepines<br>Azapirones (buspirone) | Generalized anxiety disorder |
| Hypnotic | Benzodiazepines<br>Cyclopyrrolones<br>('Z drugs') | Insomnia |
| Psychostimulant | Methylphenidate<br>Modafinil | Hyperkinetic syndrome of childhood<br>Narcolepsy |

To prevent misuse of narcotics and psychotropic drugs, recommendations have been made. These will help to reduce the unsupervised self-medication by channelizing the proper drug procurement, storage, prescribing and dispensing. Below are the few recommendations:

- Make sure to establish a medication management system that ensures pain medication and psychotropic substances shall be available who need it, with monitoring at different levels i.e., production (extempore preparation), storage, health-care (prescribing physicians and pharmacists), patients. Every hospital does not have CPOE (computerized order entry system) so there must be preprinted prescription with serial number to reduce irrational use.

- Unfortunately, there are very few and limited salts available in Pakistan due to which those patients who are in dire need of getting control substances for pain relief are unable to get medications. For example, we don't have lorazepam injection which is more potent than other short acting benzodiazepines.

- To avoid theft and misuse, raise awareness among health-care workers, parents, young people, and teachers on the consequences of misuse of prescription drugs.

- QA Audits with pharmaceutics and therapeutic committee should be done to maintain quality.

- Education for health-care providers on how to avoid, recognize, and manage non-medical prescription drug use and its effects internationally, just like antibiotic stewardship program, opioid stewardship program has been started to rationalize the usage of control substances.

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# PHARMACOVIGILANCE IN PAKISTAN

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**The World Health Organization (WHO) describes an ADR as any unpleasant, unexpected, and undesirable medication effect that occurs at normal therapeutic levels (3).**

Medication safety is a major public health concern for all nations; since there is always a proportion between the therapeutic advantages of medications and their adverse effects (1). Research suggests that adverse drug reactions (ADRs) are widespread and can result in hospitalization or even death (2).

To reduce ADR-related hospitalization and death, a strategy for ensuring the safety and monitoring of medications is required. When the medication is released into the market, it is necessary that its safety parameters are monitored through a constant channel for eliminating ADRs based on voluntary reporting for assuring patient well-being.

Pharmacovigilance (PV) is an assessment system that encompasses the identification, evaluation, understanding, and avoidance of hazardous medication effects with the intended goal to be aware of potential harm and explore the ways of reducing them (4). PV includes the entire cycle beyond the drug's post-marketing surveillance phase; which occurs for a variety of reasons, including the limited clinical trial data to a certain demographic sample, the patients having co-morbidities, polypharmacy, off-label drug usage, or variations in individuals' genetic composition (4).

## Pharmacovigilance in Pakistan:

Pakistan's PV system is still in its initial stages, and various changes have been implemented by the government to strengthen the system. Pakistan is the fifth most densely populated country, with a current population of around 227. 6 million people (5). In a nation, where the rate of over-the-counter (OTC) medication use and self-medication is quite high approximately around (25-75%) , the measures to manage this health concern are poor owing to weak restrictions.

Pakistan's GDP expenditure on well-being is quite low, at around 0.76%, although WHO recommends six percent as a minimum (5). In Pakistan, the out-of-pocket expense on pharmaceuticals exceeds 80%, the habit of going to clinics for ailments is not practiced; instead, self-medication is more prevalent. This agitation is exacerbated by a shortage of relevant personnel in community pharmacies and hospitals.

In 1968, WHO also created its Program for International Drug Monitoring, which included several member states as well as the WHO collaborating center "Uppsala." Pakistan has recently been admitted as a full member of the Uppsala Monitoring Center (UMC) in 2018 (6). The establishment of a drug surveillance system was suggested in Pakistan's National Drug Policy in 2003. However, PV efforts did not begin until 2012, when an ADR caused by a locally manufactured medication, Isotab 20 mg (Isosorbide mononitrate, batch number J093), led to the mortalities in Lahore of over 200 patients.

After the tragedy, Pakistan's Supreme Court directed the establishment of an autonomous drug regulating authority (7). Subsequently that, the Drug Regulatory

Authority of Pakistan (DRAP) Act of 2012 formed - DRAP which is among the six legislative divisions of the National Health Services Regulation and Coordination (NHSRC) and is responsible for regulating the availability, safety and quality of medical equipment and medications in the state (7).

DRAP has developed standards for PV efforts, and its provincial drug controlling division publishes drug safety alerts regularly based on data obtained from post-marketing monitoring. In 2018, DRAP arranged a unique training for DRAP officials and focus individuals from tertiary care hospitals called "Training of Trainers, Pharmacovigilance Development of Pakistan." DRAP has also scheduled basic training and talks to educate and train health-

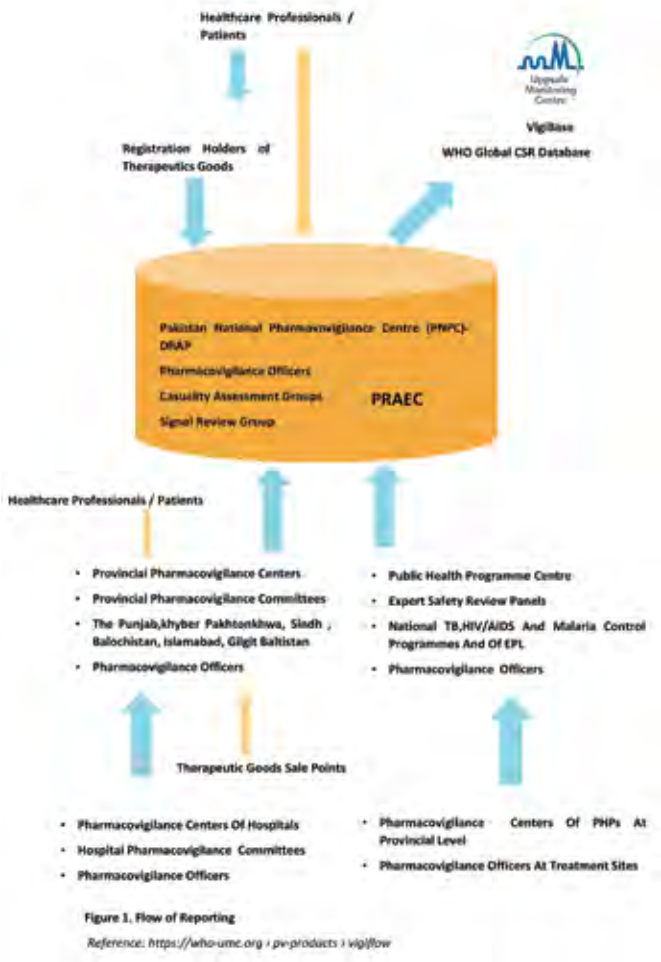



Figure 1. Flow of Reporting

*Reference: https://who-umc.org › pv-products › vigiflow*

care workers on PV. To encourage pharmaceutical firms, healthcare professionals and patients to report any ADR or adverse event, the DRAP has created a reporting form that is available on the official website called "Med Vigilance" (8).

Thereby, the National Pharmacovigilance Centre (NPC) not only contributes to WHO's goal of enhancing patient well-being in the use of medicines, but also to the evaluation of benefits, hazards, and cost-effectiveness. (Figure 1)

Pakistan's PV guiding principles reveal some flaws; it appears to be an ambitious document that seems to be promising without any execution strategy, because the policy board and ministry have concerns, including agenda prioritization, financial plan and workforce. Capacity building, national and international coalitions are more likely to boost strong stakeholders such as the pharmaceutical industry (9).

Due to a lack of appropriate PV channels, Pakistan has been unable to fulfill its part in promoting the safe use of pharmaceuticals. PV rules and recommendations are the initial steps toward increasing knowledge of PV; however, it necessitates effective dissemination and comprehension of the matter. The government has not assumed authority and responsibility for deploying PV setups in hospitals.

Patients, caregivers, and consumers are unable to report medication-related adverse events because of a variety of issues such as a lack of knowledge, a lack of counseling, the unavailability of skilled pharmacist, the absence of a role for PV in hospital settings, and so on (10).

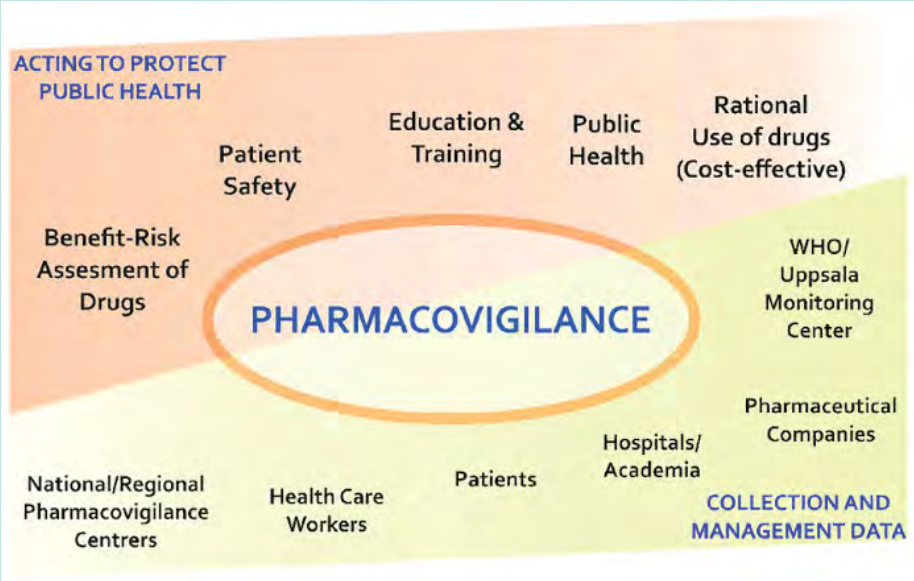
The present model of PV rules and guidelines has the following gaps:

- According to the WHO standard for the National patient safety policy model, the mechanisms or means of funding for building the PV system in hospitals and community settings are lacking.
- The proposed guiding principles do not specify what actions will have to be taken if the rules are not followed in the public and private sectors.

- A draft of PV guiding principles is being developed for the comprehension and acceptance of hospital settings and pharmaceutical industries; however, these settings currently lack PV qualified personnel (11).


## Pakistan's Pharmacovigilance Future:

The PV system requires comprehensive renovation, including a multi-stakeholder optimistic approach and standardization of methodologies to handle medications' safety concerns across the nation. As new medications enter the market on regular basis, stakeholders must implement successful PV strategies in public health programs and pharmaceutical regulation to enhance healthcare provision and to promote the safe use of pharmaceuticals; nevertheless, barriers exist in the form of financial, logistical and legal limits.




Pakistan requires multi-stakeholder collaboration and established procedures to analyze the severity, reason and preventability of potential ADRs. All stakeholders could contribute in developing a way out in the form of a standard policy execution that includes all probable actions for effective application and practice to decrease future mortalities and morbidities due to medical, hospital, industry, ministry, and academic malpractice. Pharmaceutical industry is attempting to create a consolidated group of PV specialists through its organizational platform; however, this issue is not appropriately fostered since it does not fit under the purview of business and is viewed as a supporting role. Adequate positions for PV officers should be introduced in hospitals so that the importance of community pharmacist may be highlighted besides allowing pharmacists to perform clinical pharmacy. This may likewise minimize the underutilization of trained pharmacists in hospital settings. Letters to doctors, drug alerts, media announcements, newsletters, patient education pamphlets, and personal responses to the ADR reporter are some of the techniques that can be used by the PV center and healthcare professionals to achieve this. Furthermore, healthcare professionals must be directed to take the lead and prioritize reporting of medicine safety issues in the healthcare system, which includes critical reporting areas such as what, when, how and where to include when reporting an ADR. So far, no such data on ADRs statistics from Pakistan are presented

## Table 1. Common Terms In Drug Related Events

| TERM | DEFINITION | EXAMPLE |
|---|---|---|
| Adverse drug reaction | An unpleasant or potentially harmful reaction resulting from a drug at therapeutic doses and is causally linked to it | Extra pyramidal symptoms (parkinsonism ) in a patient on chronic haloperidol use |
| Adverse drug event | An unpleasant or potentially harmful reaction resulting from a drug at any or non therapeutic dose or in an indirect manner | TCA toxicity in a patient who took overdose of amitriptyline prescribed to him as treatment for depression |
| Adverse event | Any untoward medical occurrence, during use of a drug, that is not causally linked to its use | Occurrence of malaria in a patient taking antipsychotic for schizophrenia |

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to the WHO Centre for Drug Monitoring (UMC); in this context, these initiatives would correspondingly aid in the gathering of this data.

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# A COMPARATIVE NEUROPHARMACOLOGICAL STUDY ON RATTUS NORVEGICUS DOMESTICA

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Chronic suppurative otitis media (CSOM) is a chronic infection of middle ear usually associated with perforation. Different antibiotics used in CSOM infection such as ceftazidime, ciprofloxacin, gentamicin, polymyxin B, cloxacillin sodium, cotrimoxazole, amikacin and co-amoxicillin. In CSOM infection, the most frequently found organism in Pakistan was Pseudomonas aeruginosa. This organism was sensitive by amikacin followed by with ceftazidime and ciprofloxacin. However, these antibiotics were reported to induce side effects such as CNS depression, insomnia, confusion, epilepsy and gait problems. A study was carried out on selected antibiotics to observe neuropharmacological changes induced by these drugs and their effects on different biochemical tests to find better choice of antibiotic to treat CSOM infection. For this purpose, ciprofloxacin (drug of choice for CSOM infection), co-amoxicillin (one of the most commonly prescribed drug in CSOM infection), amikacin and ceftazidime (most sensitive in population of Pakistan) were studied.

Neuropharmacological, biochemical and liver function tests along with histological examination were performed on healthy rats divided into different groups as G1: negative control (0.5ml normal saline), G2: ciprofloxacin (14.28mg/kg), G3: ceftizidime (15mg/kg), G4: co-amoxicillin (14.28mg/kg), G5: amikacin (15mg/kg), G6: imipramine (1.15mg/kg) and G7: bromazepam (0.09mg/kg). All the drugs were administered intraperitoneally to healthy rats for seven days.

Further, neuropharmacological, biochemical and liver function tests with histological studies were performed on rats induced with CSOM infection which were divided as G8: positive control (0.5ml normal saline), G9 : ciprofloxacin (14.28mg/kg), G10: ciprofloxacin with imipramine (14.28mg/kg and 1.15mg/kg), G11 ciprofloxacin with bromazepam (14.28mg/kg and 0.09mg/kg), G12: co-amoxicillin (14.28mg/kg), G13: co-amoxicillin with imipramine (14.28mg/kg and 1.15mg/kg) and G14: co-amoxicillin with bromazepam (14.28mg/kg and 0.09mg/kg).

Ciprofloxacin showed decreased in movement in open field test (17.52 %), decreased light exposure in light and dark cage activity (39.71%), decreased mobility time in forced swimming test (1.55%), delayed time in maze test (17.02 %) and traction test (30.64 %). Ceftazedime slight decreased activity in open field (6.04%), forced swim test (10.64%), exposure to the light area (25.11%) in light and dark cage activity test, delayed time traction (9.96%) and maze test (7.69%). Co-amoxicillin insignificantly decreased activity in open field (4.65%) and significant increased time spent in light by light and dark activity (22.96%). It did not effect on memory in maze test (13.58%), mobility in force swim test (3.10 %) and traction time (16 %). Amikacin showed insignificant decreased activity in open field (8.44%), mobility in forced swim test (5.32%), exposure to light in light and dark cage activity box (27.03%), delayed memory in maze test (14.89%) and increased traction time (25.32%). Reference drugs (imipramine and bromazepam) also showed decreased activities during neuropharmacological studies. Overall, results showed that ciprofloxacin had maximum effects to decrease activities followed by amikacin and ceftazidime. However co-amoxicillin showed negligible effects on behavioral changes.

Ciprofloxacin, ceftazidime, co-amoxicillin, amikacin, imipramine and bromazepam

decreased IgE levels (11.69%, 42.95%, 42.8%, 25.15, 1.88% and 27.26%, respectively), decreased serotonin levels (51.56%, 26.29%, 4.08%, 15.38, 12.41% and 16.11%, respectively), increased LT β levels (2.22%, 9.62%, 15.55%, 26.66, 37.7% and 7.4%, respectively), increased IL6 levels 10.49%, 3.49%, 9.76%, 14.51, 21.57% and 15.74%, respectively and increased IL8 levels (11.93%, 30.72%, 30.09%, 20.16%, 27.84% and 20.85%, respectively).

Ciprofloxacin, ceftazidime, co-amoxicillin, amikacin, imipramine and bromazepam increased total bilirubin (45.13%, 31.02%, 22.56%, 52.15%, 8.45% and 16.9%), direct bilirubin (30.19%, 25.42%, 12.6%, 36.4%, 6.38% and 9.5%, respectively), SGPT (68%, 44%,

28%, 16%, 20% and 12%, respectively), ALP (20.58%, 11.36%, 5.88%, 14.7%, 8.82% and 5.88%, respectively). No change was observed in GGT levels by any drug. Normal pattern in histological studies of liver was observed in all groups. Overall, neuropharmacological and biochemical studies showed ciprofloxacin induced depression, serotonin depletion and elevated liver enzymes in healthy rats. Therefore, it is necessary to be taken with precaution. Co-amoxicillin showed minimum effects on behavior changes and serotonin level; therefore, it may be prescribed in CSOM (if not resistant to the pathogenic organism). Ceftazidime and amikacin showed mild to moderate effects on behavior, serotonin depletion and on inflammatory markers, hence can be used in CSOM as second line of therapy (due to ototoxicity) if ciprofloxacin or co-amoxicillin are resistant.

Neuropharmacological and behavioral changes were observed in rats induced with chronic suppurative Otitis Media (CSOM) infection. The study showed that the infected rats showed significant decreased motor activities in open field (82.74%), decreased time exposure to light (90.9%) in light and dark cage activity, decreased mobility time in forced swim test (45.86%), delayed memory (125.36%) and increased traction time (464%) as compare with healthy rats (negative control). This behavior showed depression and anxiety in rats with CSOM infection. The drug response in animals treated ciprofloxacin and co-amoxicillin showed significant increased in number of squares covered in open field (319.14% and 276.99%), increased time exposure to the light in light and dark cage activity (36.84% and 28.94%), mobility time in forced swim test (16% and 7.29%) , decreased time in maze test (23.53% and 16.7) and decreased traction time 60.99% and 49.6%) as compare to positive control (untreated infected rats). These results showed significant improved activities in animals treated with antibiotics but not upto the normal limits (negative control). The groups received antibiotics with antidepressants which were ciprofloxacin with imipramine (G11), ciprofloxacin with bromazepam (G12), co-amoxicillin with imipramine (G13) and co-amoxicillin with bromazepam (G14) showed increased motor activities in open field (413.02%, 440.97%, 395.21% and 433.28%), increased exposure to light in dark and light activity test (197.36%, 547.36%, 194.73% and 463.15%), increased mobility time in forced swim test (44.79%, 53.12%, 23.95% and 43.05%), maze test (38.7%, 38.12%, 33.33% and 38.63%) and traction test (65.95%, 72.34%, 63.82% and 70.92%) as compare with untreated rats (positive control). Ciprofloxacin (with bromazepam) showed the maximum improvement in behavioral changes and depression in CSOM infection.

The study showed that rats induced with CSOM (positive control) showed significantly increased serum levels of immunoglobulin E (246.54%), lyphotoxin beta (321.7%) interleukin 6 (568.8%), interleukin 8 (312.07%) but decreased serotonin levels (48.42%) as compare to healthy rats (negative control). In the study, the groups treated with ciprofloxacin (G9) and co-amoxicillin (G10) showed decreased IgE levels (48.27% and 12.52%), lymphotoxin beta (56.91% and 38.74%), interleukin 6 (81.86% and 6.10%), interleukin 8 (59.52 and 37.21%), and decreased serotonin levels (25.65% and 13.67%) in contrast with untreated rats (positive control) but

significantly increased as compare to the healthy animals (negative control). The groups treated with ciprofloxacin and imipramine (G11), ciprofloxacin with bromazepam (G12), co-amoxicillin with imipramine (G13) and co-amoxicillin with bromazepam (G14) showed significant (p=0.00) decreased IgE, IL6, IL8 and lymphotoxin beta levels than positive control. The drug response produced by these groups (G11, G12, G13 and G14) for IgE levels was 67.87%, 48.09%, 31.17% and 19.78% respectively as compare with positive control. Serum lymphotoxin beta levels was decreased by 76.28%, 63.37% , 67.82% and 48.59% respectively. Serum IL6 levels were 83.47%, 82.95%, 58.41% and 21.66% respectively and IL8 levels was 68.27 %, 66.24%, 57.09% and 43.43 % respectively. Serotonin concentration was increased as 85.5%, 80.82, 47.16% and 32% by G11, G12, G13 and G14. Ciprofloxacin produced better results than co-amoxicillin and combination of ciprofloxacin with bromazepam showed decreased IgE, IL6, IL8 and lymphotoxin beta levels and increased serotonin levels up to the normal limits.

Liver function test was conducted in rats induced with CSOM in different groups. Liver function test showed increased serum concentration level of total bilirubin (91.63%), bilirubin (160%), SGPT (325%), ALP (361%) and but no change in GGT (0%) in positive control as compare to negative control. Decreased concentration of liver enzymes were observed by ciprofloxacin (G9), co-amoxicillin (G10), ciprofloxacin with imipramine (G11), ciprofloxacin with bromazepam (G12), and co-amoxicillin with imipramine (G13) and co-amoxicillin with bromazepam (G14) with drug response 24.26%, 42.65%, 55.88%, 25.01%, 47.06% and 0.0%, respectively for total bilirubin, 50%, 61.5%, 61.5%, 53.84%, 61.5% and 57.69% respectively for direct bilirubin, 58.989%, 86.48%, 93.24%, 86.48%, 86% and 91.79% respectively for SGPT and 41.08%, 96.81%, 92.99%, 96.81%, 96.81% and 89.17% respectively for ALP. However, only ciprofloxacin (G9) increased GGT with 62.5% drug response. This may be due to hepatotoxic effects of ciprofloxacin by itself. In histological examination, aggregation, inflammation and infiltration with dilation of the vessels was observed in rats with CSOM. Ciprofloxacin and co-amoxicillin showed slightly better pattern as compare to the positive control but poorer than negative control. The groups received antibiotics with antidepressants presented approximately the same pattern of inflammation with aggregation. Minimum aggregation and inflammation is presented by ciprofloxacin with imipramine and maximum by ciprofloxacin.

Overall, these results showed that combined therapy of antibiotics with antidepressants brought significant improved behavioral deficits; normalize biochemical markers and liver enzymes concentration as compare to only antibiotic therapy.

It is, therefore, concluded that ciprofloxacin, ceftazidime, co-amoxicillin and amikacin produced depression in animal study. This depression was maximum with ciprofloxacin and negligible with co-amoxicillin. However, the use of co-amoxicillin is being redistricted due to high resistance in adults. Whereas, when these antibiotics administered in CSOM infected animals they reduced infection maximum by ciprofloxacin. The depression reduced in by ciprofloxacin was as compare to positive control but not reduced as compare to negative control. In human study, ciprofloxacin reduced infection with decrease in depression as compared to positive control. It is worth telling that only combined therapy of antibiotics with antidepressant/ anxiolytic helped in attenuation of depression during time of infection in animal study. Further clinical trials are necessary to explore effects of antibiotics with antidepressant/ anxiolytic in CSOM.

# HEALTH TECHNOLOGY
## 100 YEARS OF INSULIN DISCOVERY

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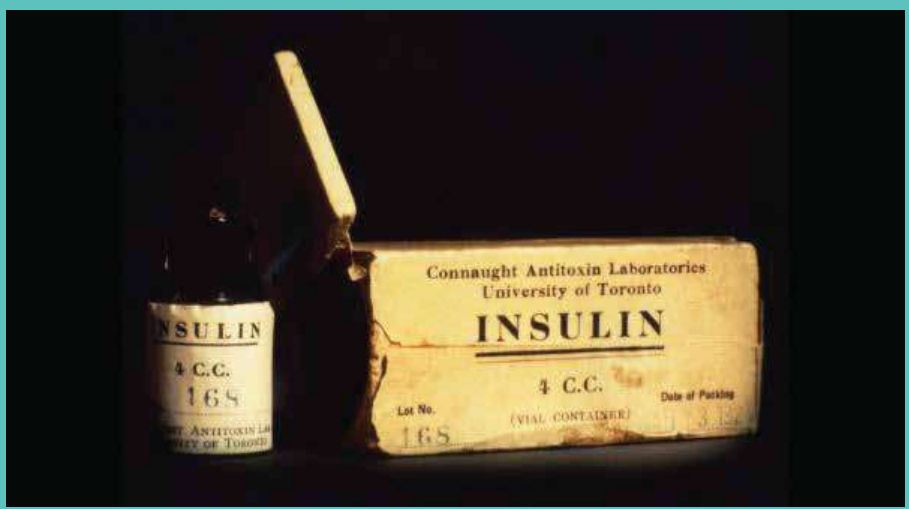
Insulin is an essential hormone in the human body, which is secreted by the beta cells of pancreas. Insulin helps the blood glucose enter cells of the human body, where glucose is the chief source of energy, and subsequently life.

Back in the early 1900s, when insulin was not discovered, children with Type 1 Diabetes, wherein there is an absolute deficiency of insulin hormone, used to die. No insulin meant no access for glucose into the human body cells. The cells starved to death, and the children with Type 1 Diabetes were left to die.

Insulin was first discovered in 1921 by Sir Frederick G Banting, Charles H Best and JJR Macleod in Canada. In January 1922, a 14 year old boy, Leonard Thompson, was the first human to receive insulin. For the first time in the history of mankind, children with Type 1 Diabetes were not left to die, they had a life! The mass production of insulin began in May 1922. Year 2021 marked 100 years to the discovery of insulin. Unfortunately even today, people still do not have an easy access to this vital hormone.

Diabetes has two main types. Type 1 Diabetes is usually seen in children and young adults. This type of diabetes quickly evolves over a few weeks. There is complete insulin deficiency. The only treatment is insulin administration from outside. For people with Type 1 Diabetes, insulin is their lifeline. The other type of diabetes is Type 2 Diabetes. More than 90% of diabetes is Type 2. This diabetes is rapidly increasing across the globe and the main reason is an unhealthy lifestyle and rising obesity. In Type 2 Diabetes, initially there is sufficient insulin but there is resistance to insulin. So in the early course of disease, usually oral medications are used to control blood glucose levels. As months and years pass by, the insulin secretion also declines, and more and more Type 2 Diabetes patients need insulin from outside. There is another variety of diabetes known as gestational diabetes, which affects one in seven pregnant women. Most of these women need insulin to manage their gestational diabetes. Insulin is also used to control blood glucose in most diabetic patients who are admitted in hospitals. Undoubtedly, this vital hormone discovery has made a hugely positive and lively impact on the management of diabetes mellitus. Yet, even after 100 years of insulin discovery, both access to insulin and the usage of insulin is far from where it should have been.




In Type 1 Diabetes, insulin is the mainstay of treatment. It has to be started right at the outset. In Type 2 Diabetes, usually medications are started initially, and insulin has to be started when medications alone can no longer control blood glucose levels. But starting a patient on insulin is not an easy process. It is a huge change in the lives of the patients. There are many barriers to insulin treatment, both at the level of the physicians as well as the patients. Physicians usually have a lot of patients to see in their clinics, counselling the patients to take insulin and then teaching them the correct method can be time consuming and taxing. Most practitioners in Pakistan do not have trained diabetes educators to assist them in their clinics. Physicians know that initiating insulin treatment may require

more work on their part, they'll need to educate the patient more and the patient might still have problems in the initial few days to weeks. Patients on the other hand also fear insulin. The myths associated with this hormone are numerous. Many patients consider insulin as a last stage of treatment of diabetes, which of course is untrue. Others are worried about injections, while some are afraid they may be bullied by family and colleagues. In short, most patients want to avoid insulin, and some physicians also want to defer the insulin treatment. This delay at the level of the physicians and the patients eat up many months and years before insulin is actually started. Uncontrolled diabetes during all this time can bring numerous complications to the patients. The whole focus of modern day diabetes management is to educate both practitioners as well as the patients that insulin is a safe and effective treatment for diabetes and should be initiated a lot earlier in the course of diabetes management.The main side effects of insulin treatment are weight gain and hypoglycemia (low blood glucose level). With proper education to the patient about diet, both weight gain and hypoglycemia can be minimized.

Insulins can be broadly categorized as basal and bolus insulins. Human pancreas is producing small quantities of insulin at all times, regardless of meal intake. This insulin is termed as basal insulin. When we eat food, there is a surge of insulin release from pancreas. This surge lasts for a few hours to take care of the glucose in the meal. This insulin is termed as bolus insulin. With every meal, this surge of insulin helps cater to the glucose that enters the blood stream. If we need to give insulin from outside, and we are to mimic this natural insulin physiology, then we need two types of insulins. We need a basal insulin with a half-life of 24 hours to mimic the small amounts of insulin that is secreted by pancreas round the clock. We need bolus insulin with a half-life of 4-8 hours, three times a day, to mimic the intrinsic surges of insulin that naturally comes with meals. This means that if we mimic the pancreatic function from outside source of insulin, we need 4 insulin injections per day; 1 basal insulin injection and 3 bolus insulin injections. There are also pre-mixed insulins, which have both basal and bolus insulins mixed together. These pre-mixed insulins can be given 1-3 times per day.

Insulins can also be divided into human and analogue insulins. Human insulins are cheaper while the analogue insulins are 2.5 times more expensive. The analogue insulins have lesser chances of hypoglycemia and they are taken immediately before meals, while human insulins have more chances of hypoglycemia and they are taken 30 minutes before meals. Though analogue insulins are more advanced, they are way more expensive. With a proper diet schedule, the hypoglycemia risk with human insulins can be minimized. In Pakistan, which is a developing country, human insulins should be prescribed more than analogue insulins. This will be cost effective for our patients and also prevent our country's foreign exchange as most of the insulins available in our markets are imported from the United States of America and Europe.

100 years ago when insulin was discovered, it must have been a remarkable breakthrough in the management of diabetes at that time. But even today, access to insulin treatment is not at all adequate. Cost is a major factor. Physicians should try to prescribe human insulins more than analogue insulins to make it more cost effective for the patients. More education is required for both practitioners as well as patients so that insulin treatment can be started well in time, to prevent the notorious complications of diabetes mellitus. Let's use this vital hormone in a way that makes life better for our patients.

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# PARACETAMOL
## : A STEALTH KILLER

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Paracetamol is a non-prescription popular pain killer which has almost become the victim of its own success. It is available in different brand forms such as Panadol®, Tylenol®, Dafalgan®, Empaped®, Antalgic®, Dolorol®, Napamol®, Painamol® and many others. Paracetamol is used in daily life to provide relief from aches and pains. Paracetamol causes Liver toxicity when taken in high doses.

In pains killers, Paracetamol and NSAIDs are considered, "bearing a low risk of addiction, tolerance, dependency and withdrawal". When paracetamol is used as combination therapy with opioids, "rebound headaches" are seen generally, that are also known as medication overuse headaches. Hepatotoxicity is very unlikely if less than150 mg paracetamol per kg body weight has been ingested. Paracetamol has a narrow therapeutic index, due to this reason it can cause toxicity in levels which are beyond toxicity index.

Paracetamol poisoning increased from 1960's; it is one of the common self-poisoning cause. Mortality due to paracetamol poisoning has increased extensively since then .There are different ways for reducing its toxicity, keeping in consideration its harmful effects, serious consideration should be given to changing the legal status of paracetamol. Restriction on prescription only rather than over the counter avalibility will restrict its harmful effects (Sheen, J.F .et al.,2007). Paracetamol in therapeutic doses carries little risk of adverse events (Jones, A.L. .et al.,2007). Plasma half-life of unchanged paracetamol was evaluated in 30 patients with over dosage of paracetamol & liver necrosis was observed in 17 patients who developed fatal hepatic coma. (Prescot , P.R. et al., 1971)

Liver toxicity is a major problem during drug development and for the use of many known drugs. Paracetamol toxicity is the main reason for hepatic failure in the US and Britain .When evaluated, it is observed that the mechanism by which paracetamol induced toxicity occurs is through mitochondria, as the mitochondria are critical targets for drug toxicity, either directly or indirectly through the formation of reactive metabolites. The consequence of these modifications is generally a mitochondrial oxidative stress, which results in structural changes and alterations in the proteins and mitochondrial DNA and, eventually, to the opening of mitochondrial membrane permeability transition (MPT) pores. MPT pore formation results in a collapse of mitochondrial membrane potential and stoppage of ATP synthesis. In addition, the secretion of inter-membrane proteins, such as apoptosis-inducing factor and endonuclease G, and their translocation to the nucleus, cause nuclear DNA fragmentation. Altogether, these events trigger necrotic cell death. On the other side, the release of cytochrome c and other proapoptotic factors from mitochondria can cause caspase activation and apoptotic cell death. Drug toxicity can also result in an inflammatory response with the formation of reactive oxygen species by Kupffer cells and neutrophils. If improperly detoxified, these extracellular produced oxidants can diffuse into liver cells and trigger mitochondrial dysfunction and oxidative stress, which then induces MPT and necrotic cell death. (Harrison , D.J et al., 1998)

There are many individuals who have no symptoms of paracetamol poisoning in the initial 24 hours after over dose. In some cases it is observed that individuals do have some undiagnosed symptoms E.g.: Pain in abdomen, nausea and vomiting .But as the disease progresses it is seen that the signs of liver necrosis are observed. This involve low sugar level in blood, also signs of liver failure may develop; low blood pH, easy bleeding, and hepatic encephalopathy. There are some symptoms which subside, but if untreated they can also result in death. Damage to the liver, or hepatotoxicity, results not from paracetamol itself, but from one of its metabolites, N-acetyl-p-benzoquinoneimine (NAPQI;also known as N-acetylimidoquinone). (Prescot , P.R. et al., 1971) NAPQI depletes the liver's natural antioxidant glutathione and directly damages cells in the liver, leading to liver failure. (Dally , F.F et al., 2008)

The dose at which Paracetamol causes toxicity is variable. Paracetamol causes poisoning in adults at the dose above 4 gms. Dose higher than this is enough to

cause poisoning. Generally in adults, single doses > 10 gms or 200 mg/kg of total bodyweight, have a reasonable likelihood of causing toxicity. (Dart , R.C et al., 2006) Taking this amount on regular basis result in increase in the alanine transaminase in the liver .This increase in alanine level is usually three times more than normal (Voppalanchi , R.L et al., 2003). Studies have shown that significant hepatotoxicity is uncommon in patients who have taken greater than normal doses over 3 to 4 days. (Dally , F.F et al., 2008) In adults, a dose of 6 grams a day over the preceding 48 hours could potentially lead to toxicity, (Dally , F.F et al., 2008) while in children acute doses above 200 mg/kg could potentially cause toxicity. (Slattery , J.T et al., 2006)

Acute paracetamol overdose in children rarely causes illness or death, and it is very uncommon from the studies that those individuals who take Paracetamol for 3-4 days with the same amount, usually do not experience any toxicity.

It is not usually in children to have deaths with paracetamol toxicity, also it is not commonly seen that their drug level reaches to a level that requires treatment. IV doses are smaller (Larson , A.M et al., 2008) .There are some individuals in which it is rarely seen that toxicity occurs in normal dose. Children to have levels that require treatment, with chronic larger-than-normal doses being the major cause of toxicity in children (Sheen, J.F .et al.,2007). Intravenous doses should be smaller than those taken orally, all other things being equal.

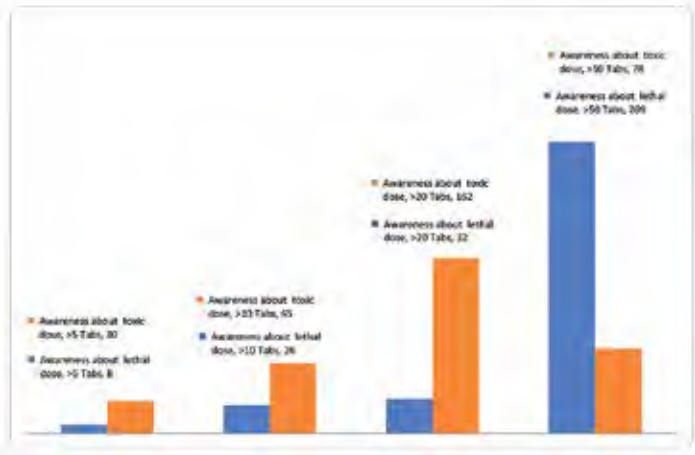
Although children experience less hepatotoxicity than adults with equivalent toxic paracetamol plasma concentrations, adolescents develop hepatotoxicity within the range associated with liver damage in adults. The minimum toxic dose in adults is 125 mg/kg, or approximately10-15, 500 mg tablets in the age range studied. Lethal hepatotoxicity is common at a dose of 250 mg/kg

or 20-30,500 mg tablets for the study population.
A study carried out in Pakistan reports that after ingestion of Paracetamol there is increased risk for hepatic issues, and renal complications may also arise from them after delay of 8 hours from its administration (see Table 1).This can be reduced by giving timely antidote i.e N-acetylcysteine. If therapy is given within 8 hours then it can prevent serious injuries. Although, N-acetylcysteine, has some adverse effects and is not very

economical. Also administration of N-acetylcysteine requires admission to hospital, so it is not wise to administer in all the patients with overdose of Paracetamol. Study proves, Paracetamol is extensively utilized in the general population. The frequent reason for the use of drug includes its over the counter availability (OTC) and confusion regarding its side effects. Authors propose awareness programs on use of medicines in schools and public places.

Table 1:Lethal dose and Toxic dose awareness survey.

| No of tablets | Awareness about lethal dose | Awareness about toxic dose |
|---|---|---|
| >5 Tabs | 8 | 30 |
| >10 Tabs | 26 | 65 |
| >20 Tabs | 32 | 162 |
| >50 Tabs | 269 | 78 |



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4 Department of Pathology, University of Edinburgh, Medical School, Teviot Place, Edinburgh EH8 9AG, UK; Department of Histopathology, Sandringham Building, Leicester Royal Infirmary, Leicester, LE1 5WW, UK;angus.mcgregor{at}uhl-tr.nhs.uk. Liver death and regeneration in paracetamol toxicity.A H McGregor

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# AN UNHOLY ALLIANCE

**Dr. Zafar Mirza**
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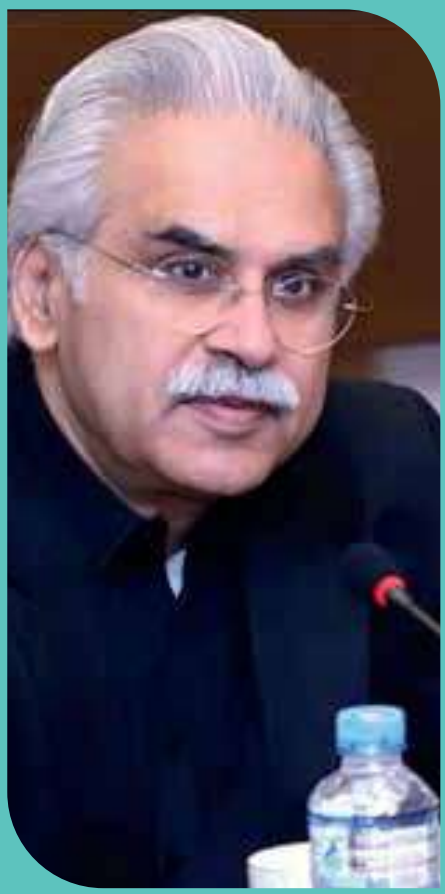
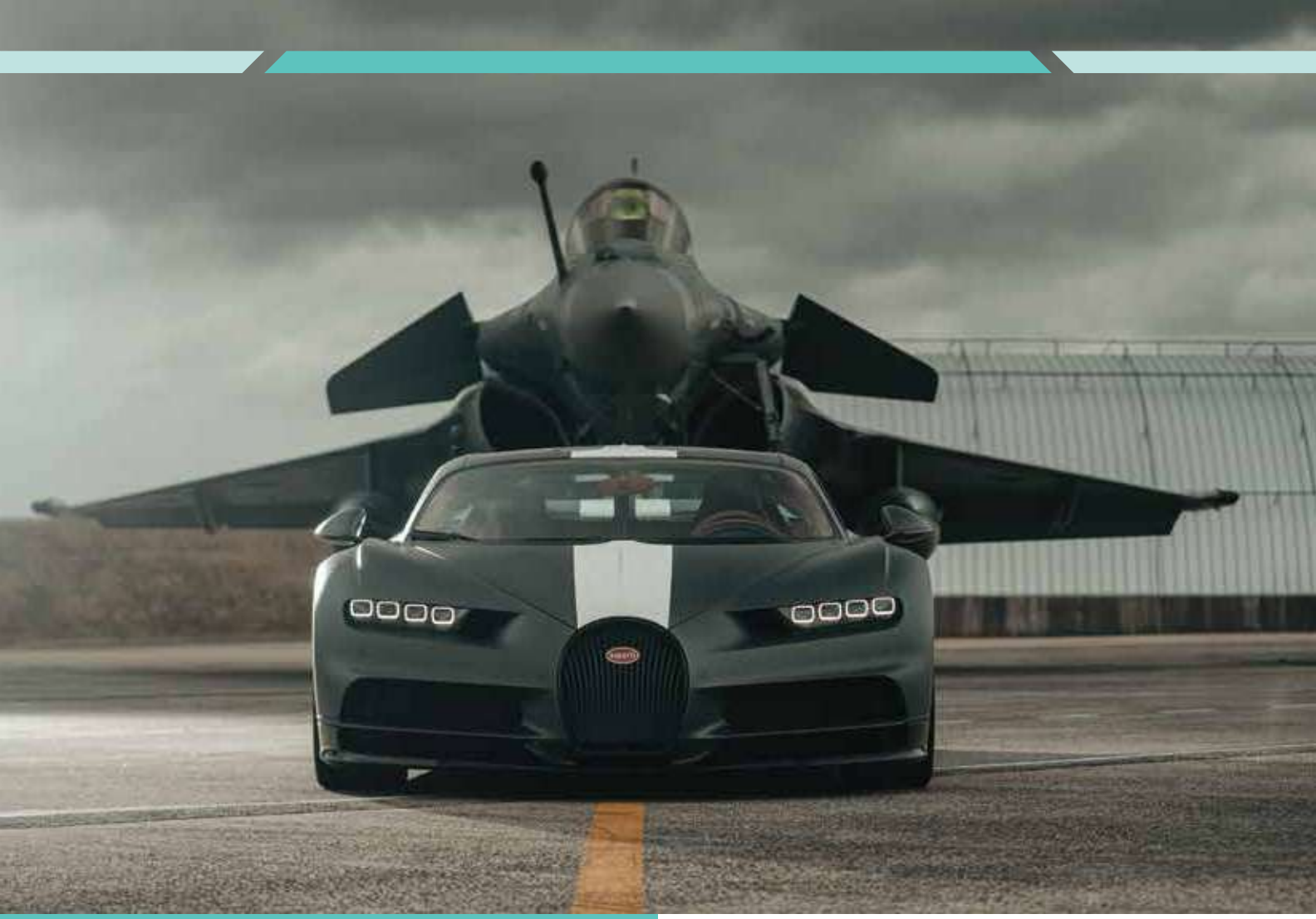


THERE is an unholy alliance working against the interests of patients. Highly unethical dealings go on between the pharmaceutical and health technology industry and doctors and other health professionals. Last year, the Journal of the American Medical Association reported that 26 pharmaceutical companies paid around $33 billion in fines between 2003 and 2016 in the US. These financial penalties were slapped by the US authorities on account of various illegal activities, such as providing kickbacks and bribes, knowingly shipping adulterated or contaminated drugs to pharmacies, and marketing drugs for unapproved uses.

Transparency International reported on the corruption in the pharmaceutical sector in 2016 with the support of UKAid. It stated that in the US alone the pharmaceutical industry spends an estimated $42bn annually on promotional activities that target doctors. This is equal to an average of $61,000 per doctor.The WHO in 2010 reported that medicines account for three of the top 10 sources of inefficiency in the health system, and corruption is a leading source of inefficiency.Most of this kind of research takes place in the US and Europe. Some of the multinational corporations are also active in most low- and middle-income countries. Despite stringent regulatory authorities and generally higher societal consciousness about the rule of law in high-income countries, the companies do not shy away from indulging in these highly unethical activities. What would the same companies do in poor countries where the relevant laws are absent or weak, regulatory authorities lack capacity, and corruption is an accepted way of life? Local pharmaceutical companies join the MNCs in corrupting medical practice. Gullible patients pay through their nose as they buy unaffordable medicines which may not be needed in the first place or for which equally efficacious but cheaper alternatives are available. Sales representatives are given targets and they are dependent on medics for prescribing their medicines. Companies producing the same medicine compete for popular doctors through offering bigger and better incentives, which have moved from bad to worse to ugly. The word 'unethical' has become incapable of conveying what is going on in the medical marketplace.I recently sat down with a group of young researchers who were concerned about this situation and were struggling to choose effective interventions to address this imbroglio. In their scoping work, they had discussed and observed what was going on between the marketing tigers and the ever-willing doctors. They spoke to both sides — the sales representatives and doctors. Their findings and examples from elsewhere are not just unethical but also horrifying: A grand valima of a busy doctor's son was entirely sponsored by a pharmaceutical company. The whole family and a number of friends of a popular surgeon were taken to a popular Southeast Asian beach resort for a weeklong holiday; everything was paid by a company. A sales representative told a doctor he could not give him the cash demanded but could provide an AC; the doctor told the rep to send the AC to a particular AC shop and the doctor received the money from the AC retailer.A valiant sales rep can pay for car service for a doctor, refurbishing his office, expensive private school fees, utility bills and any other imaginable expense. Depending upon individual taste and preference, some doctors have allegedly accepted drinks and more — including a full umrah package from the pharmaceutical industry. Umrah packages for spiritual cleansing at the cost of suffering patients who can't afford the cost of the medicine — irony needs to be redefined. All this is investment for companies with huge returns on investment.

The usual argument that high prices charged by pharmaceutical companies is to recoup the high expenditures they incur on R&D is flawed. Nine out of the 10 largest pharmaceutical companies spent more on marketing than on R&D according to one study. So, high prices of medicines are also due to large sums spent by companies on the marketing of their products, a very big part of which goes into incentivising the doctors to liberally prescribe their products. And the R&D spending argument does not apply to local pharmaceutical companies, they are quite clean on this count.How to address all this? From the global to local level, the pharmaceutical industry does not like any restrictions on its marketing practices. Despite its efforts, the WHO has not been able to produce any hard law other than a toothless and outdated Ethical Criteria for Medicinal Drug Promotion in 1988. The US and Europe have introduced stringent regulations in this connection.

[1]Article originally published in DAWN 03 DEC, 2021, Reprinted with permission.



In 2014, the Physician Payment Sunshine Act was passed in the US, which requires companies to disclose in an online database payments of over $10 that they have made to doctors. Closer to home, the art of unethical marketing has thrived beyond imagination and there is hardly any regulation. On Nov 17, the government of Pakistan finally issued the Ethical Marketing to Healthcare Professionals Rules, 2021, through the Drug Regulatory Authority of Pakistan. One of the stipulated functions of DRAP is to "monitor and regulate the marketing practices so as to ensure the rational use of drugs…". It has taken the government nine years to come up with these rules after the Drap Act of 2012. The rules are not only late; they are also lame and quite out of sync with the times. Medicines are now being promoted and sold online but these rules do not bother about this. The weakest parts of the rules deal with enforcement, contravention and punishment.

These are very vague and non-committal. How they are going to be implemented is not clear and there is justified lack of hope about them changing anything on the ground. Nevertheless, now we have rules for ethical marketing. Their implementation needs to be monitored and reported regularly by civil society organisations, academia and the media. This can only ensure further strengthening of the rules and eventually some hope for impact. The reformed Pakistan Medical Council also needs to become active in this ignored area.

# HEALTH ECONOMICS IN PAKISTAN:
## A SITUATION ANALYSIS

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Health is not only absence of disease, but also implies a physical and mental wellbeing. Health Economics (HE) makes it possible, by informing how to realize unlimited, and sometimes alternating, health care needs with limited resources.

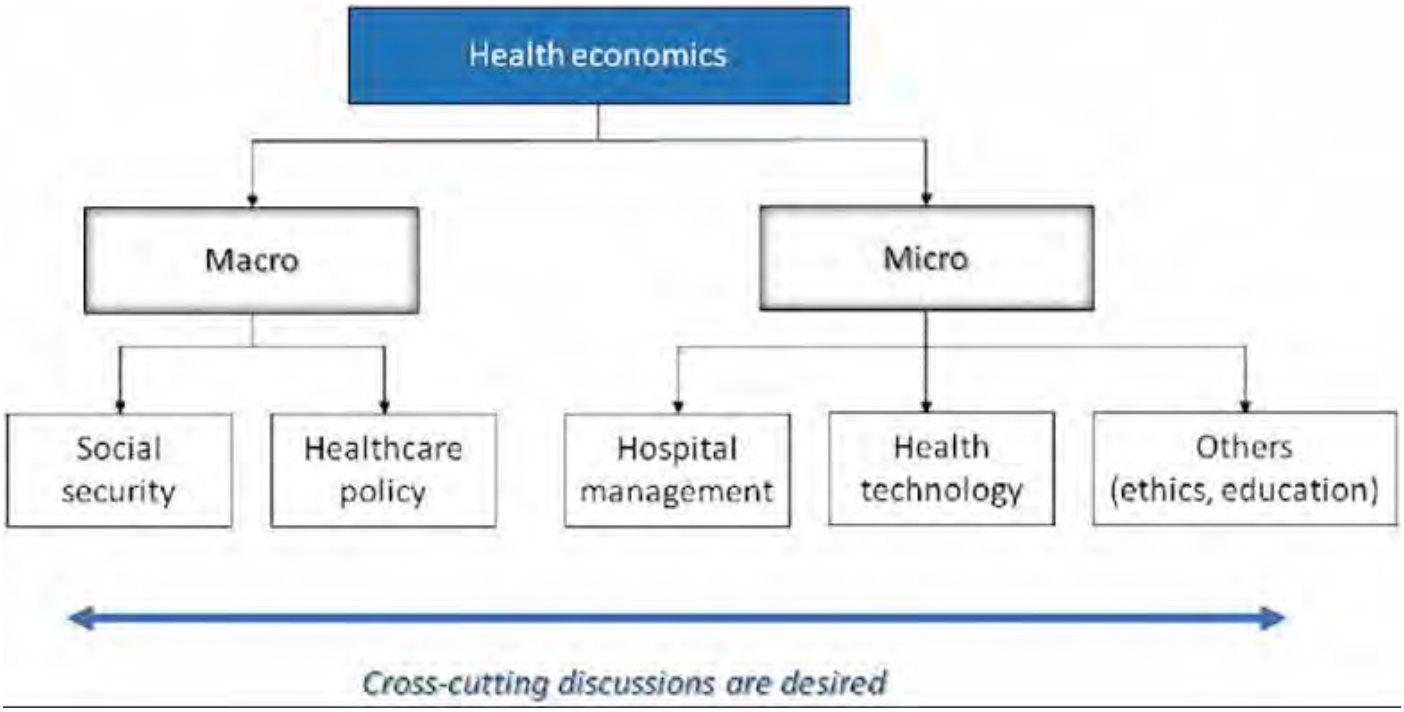
In a hypothetical situation if or when we have unlimited resources to invest on health care, there would be no problem. We would have spent major part of our resources on wellbeing. But the problem is that resources are scarce, and health care providers or managers have to make choices related to resource allocation. With limited budget, economies have to decide how many health professionals we can afford to have, how many healthcare units we can afford to establish, do we have sufficient funds to subsidize the medication, how much amount government should spend on general healthcare, all such decisions are based on the basic knowledge of health economics.

Health economics serves as a tool for comparing the costs and benefits of different interventions and programmes. Health economic tools gives us alternate ways to utilize our resource effectively through interaction of healthcare utilizers, providers, and agencies- taking their individual perspective into account. There are limited opportunities in Pakistan for training and development in health Economics.


A weekly health economics research interest and peer support group has been launched. It is a joint collaboration between Pakistan institute of living and learning and Global Mental Health Cultural Psychiatry research group from University of Manchester. This group is supported by number of National & International institutions such as University of Glasgow, Sheffield Hallam University, Pakistan Institute of Development Economics and others.

Health sector is one of the most uncertain enterprises among all due to the influence of numerous external factors. The benefit derived from the health is also indirect in terms of cost utility. The person, when healthy, will contribute to general economic growth. The benefit therefore, although essential, is not directly obvious. The chronic diseases cases are very common and require huge resources in this sector. Hence, experts recommend to exert more effort and resources on prevention and awareness before diagnosing diseases. The challenges associated with health are massive and require input from all disciplines. Unique challenges often require large funds to find a solution. Several attempts and experiments may be required, which are not cost effective in medium to long-term. That is why, annual budgeting for the health expenditure is very critical across the globe.

Challenges of low and middle income countries (LMIC) such as Pakistan are different from high income countries but the concept and models of economics are the same. Pakistan is the sixth most populous country in the world but




unfortunately it stands at the 146th rank on human development index. Pakistan was not able to meet the Millennium Development Goal, like some other Low-and-Middle Income countries, but is making remarkable attempts to reach the sustainable development goals (SDGs). Country is aspiring to become an Upper Middle Income country by 2030. Pakistan has to reduce the maternal and infant mortality rates as well as all the morbidity and mortality caused by epidemics of communicable diseases, injuries and accidents through its mixed health care delivery system. Both formal and informal health care markets are fully functioning in Pakistan. Federal and Provincial ministries are supporting the healthcare system along with the private health care providers. A large setup of Non-Governmental Organizations (NGOs), homeopathic, and hakims are also working with informal setup of pir faqeers and spiritual healers.

Health care users belong to different setups in Pakistan, some of them are able to pay out of pocket for services while majority has to borrow to pay their medical bills. Out of pocket expenditures and users fee are the major funding source for Pakistan's healthcare market. Some of the emergency health needs are covered with grants and foreign funding but these are only provided on certain occasions. With limited financing, it's a challenge for the government of Pakistan to fulfil the needs of poor segment by allocating the budget efficiently. Therefore, involving health economist in decision making is important. Even with limited resources, and continuing situation of pervasive COVID-19, Government of Pakistan is still making effort to facilitate the healthcare system. Not only awareness campaigns have been initiated, protection schemes such as Sehat Sahulat health program (SSP) are also initiated with some benefit. In the current fiscal year 21.7 Billion Pak. Rupees have been allocated to healthcare. As Government of Pakistan is trying to maintain an affordable healthcare system, it's highly recommended to track and evaluate the quality and accessibility of the on-going projects. Health economists can provide the guidelines for quality evaluations. Despite a diversified healthcare profile and continuing evolution in healthcare system, Pakistan's major issue is high population growth, maternal and infant mortality associated with high level of trauma, and rising burden of illness.

Depressive disorders with 3.13% (2.25 – 4.24), anxiety disorders 1.7% (1.21 – 2.3), and schizophrenia 0.97% (0.68 – 1.25) are major contributors of disabilities (Disability Adjusted Life Years – DALYs) in Pakistan. Increasing mental and physical illnesses are also causing greater economic burden on the community as the burden of diseases which was estimated to be 250 billion PKR in 2006 has become 620 billion PKR in 2020. COVID-19 pandemic has worsen the situation when thousands of people are struggling with their physical and mental health issues, and government is unable to meet the healthcare needs. Millions of people lost their jobs due to lock down, social isolation caused social, mental, and economic hardships for the population. To handle such situations, we need specific models, which relate to Pakistan's context and can provide guidance on how much should be invested on different interventions to minimize and identify the burden of different illnesses.

A health evaluation study by a research group determined the cost effectiveness of Learning Through Play (LTP+) for maternal depression and Culturally Adapted Manually Assisted Brief Psychological Intervention (CMAP) for reduction of self-harm in Pakistan. Studies suggest that 16,254 US$ are required to gain a single QALY for the self-harm patients in Karachi. Moreover, findings can also be used in other evaluation techniques (Cost Effectiveness Analysis) which the LTP+ study suggests that US$ 2,590 are required to gain a single QALY for depressed mothers in Karachi. In larger and more extensive

CMAP2 studies, the preliminary findings suggest that US$ 2,328 is the cost that will gain a QALY for a self-harm patient in Pakistan. Different countries have set their threshold level of cost to gain single QALY such as UK – The National Institute for Health and Care Excellence (NICE): £20,000 to £30,000 / QALY, Canada – Canadian Agency for Drugs and Technologies in Health (CADTH): CA$ 50,000 / QALY and USA – World Health Organization (WHO): US$50,000 - US$80,000 / QALY. This threshold varies from country to country but it has been also indicated that threshold should be equal to country's overall GDP per capita. For calculating this cost calculation can provide systematic computation of treatment costs which can help in making the health-care decisions. Preliminary attempts have been made to compute the treatment cost of few diseases in Pakistan (2020) such as, burn care treatment cost is PKR 235,788/-, diabetes treatment cost is PKR 93,298/- PA. Difficulties arise when one has to make choices with limited resources, in Pakistan. Everyone, whether an individual who is a student, professional or even a woman making her household decisions has to face the problem of rationing. Getting most out of limited resources is the ultimate result of effective planning. Pakistan also needs to plan its resource utilization in a careful and effective way to maximize the well being of its masses. But to obtain this goal we need to promote awareness. Gaps in knowledge and evidence base which are limiting our growth needs to be identified. Though there has been tremendous development in education sector, health economics has yet to be recognized as a separate discipline in Pakistan.


We need to promote health economics as a separate domain so that we can have professional advisors with expertise. Only by bridging this capacity gap in our health sector, we can boost the working of our healthcare sector. Increasing awareness about the importance of understanding healthcare cost effectiveness and how economic studies can address health challenges with possible cost effective solutions. This is the first step towards building stringer health infrastructure. In summary, health economic evaluation can help address many healthcare challenges using National and Provincial financial resources efficiently to inform policy and utilize the health budget as effectively as possible. Acknowledgment: We would like to acknowledge HE group members from Pakistan Institute of Living and Learning (PILL) and supervisors from UK – Prof. Nusrat Husain, Dr. Anil Gumber, Prof. Anita Patel, Dr. Tinevimbo Shiri, Dr. Nasir Iqbal and Prof. Rod Taylor for such a remarkable support in the completion of this Article. This has been partially funded by the medical research council (MRC), Department of International Development (DFID), National Institute of Health Research (NIHR) (MR/R022461/1). Global challenges Research Fund (GCRF) SAHAR-M (NIHR) (MR/PO28144/1) and Grand Challenges Canada (GCC, LTP+DADS, R-TTS-2106-39652). The views expressed in here are those of the author(s) and not necessarily those of the funding bodies or the sponsor.

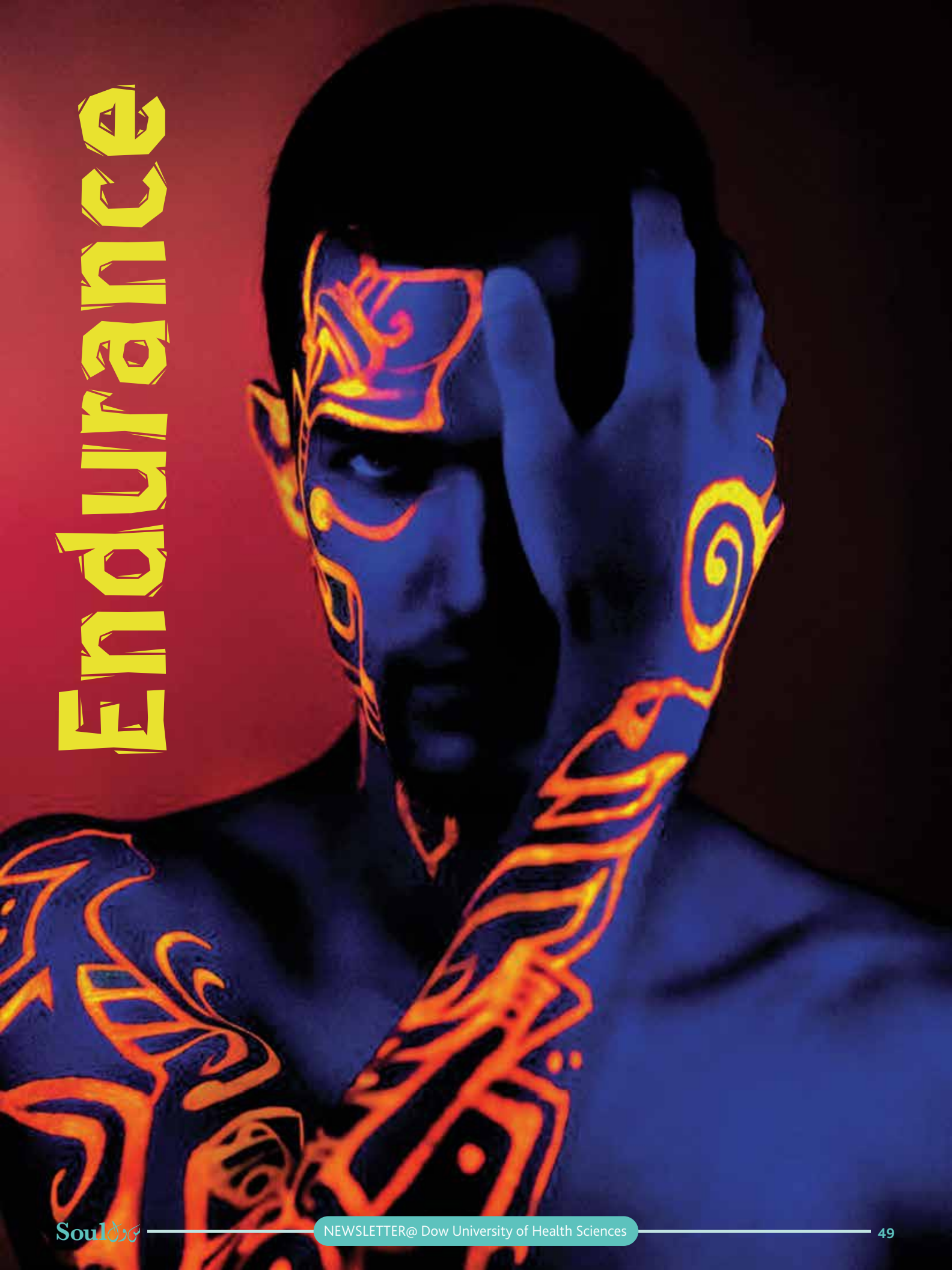

Addiction


Greed

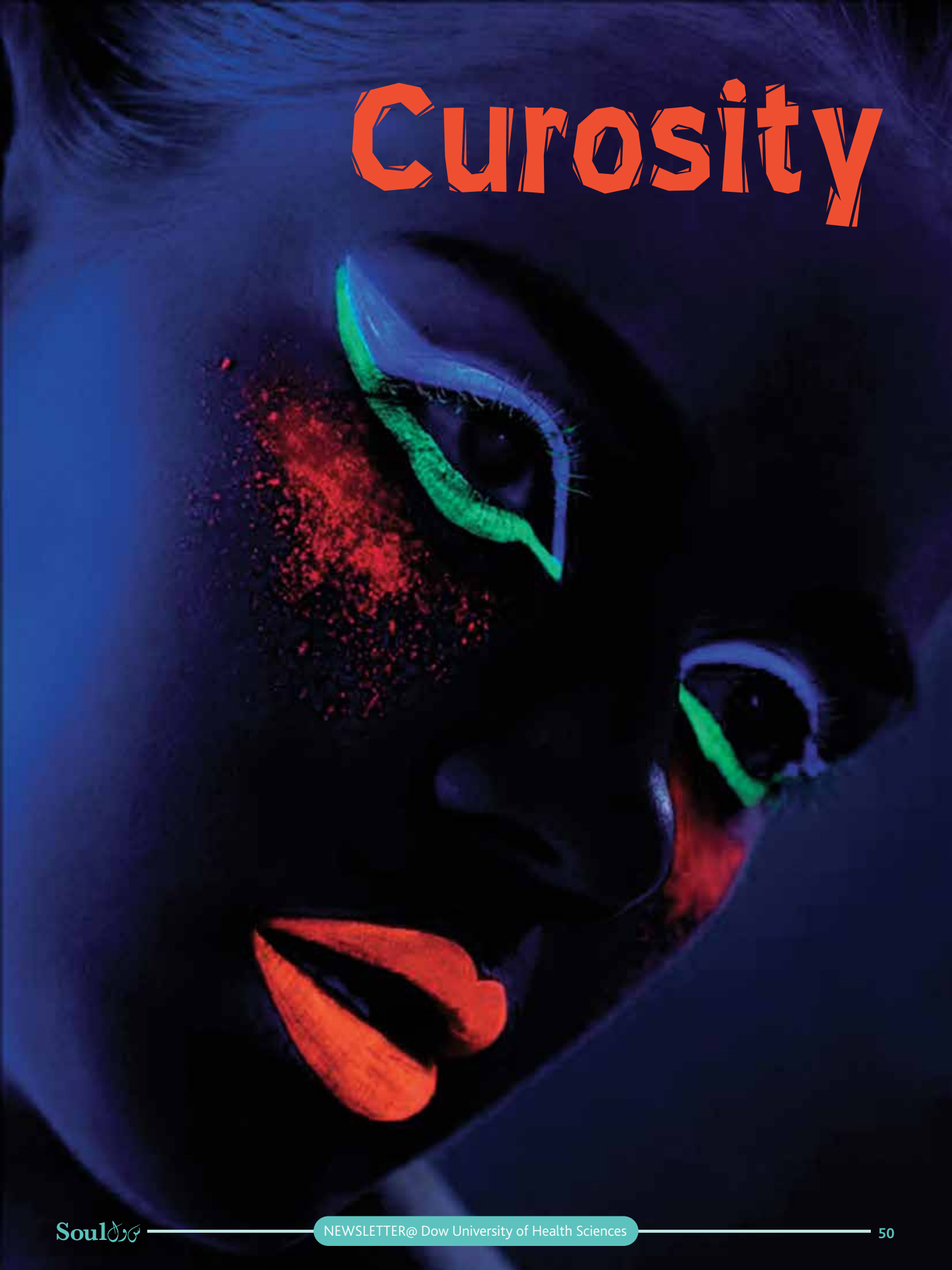
# Deceit


Discernment

# Endurance



# Curosity



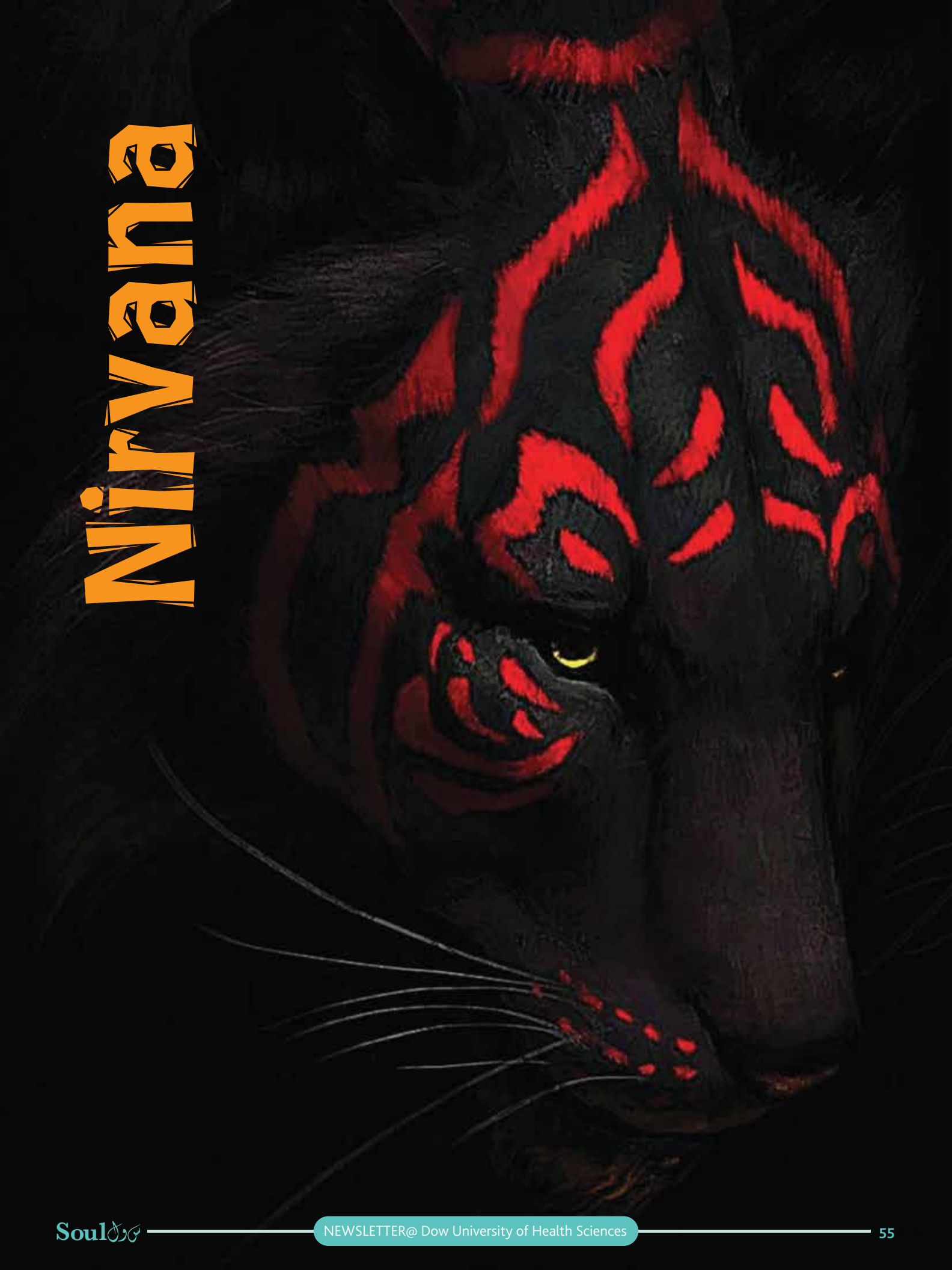
# illumination


Love

# Lust

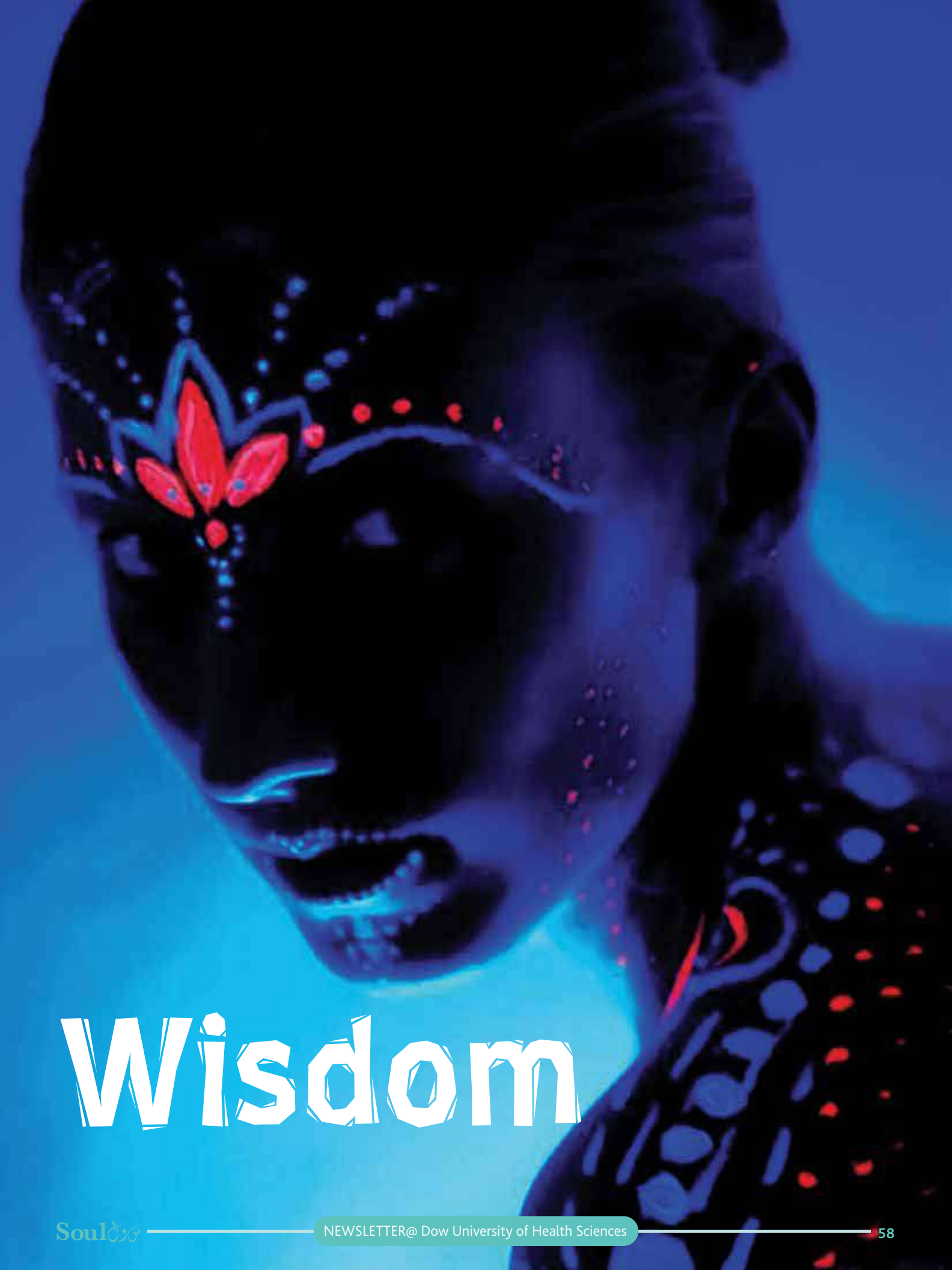
# Modesty

# Nirvana




Perspective

# Rage



# Wisdom

# Handbook of Clinical Trial Research:

## Theory & Practice

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# Section 01

# THE CLINICAL TRIALS:
## BEGINNER'S GUIDE

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Randomized control trials are considered to be gold standard in terms of clinical decision-making. The three features of RCT which confers advantage over other uncontrolled experiments are randomization, blinding and a placebo-control group[1,2,3]. Through randomization, investigators ensure that characteristics, which are known (like socio-demographic characteristics) and those that are unknown (genetic predisposition, immune status, etc.), are balanced between the two groups. However, randomization only ensures balance when the sample size is large enough[4].Sample size calculation is not only a matter of good science but also has to do with practicalities of time and resources.[5] Though it is unethical to do an under-powered study, subjugating the participants to unwarranted risks, it is equally undesirable to waste resources once the research-question has been answered. In a clinical trial small sample does not ensure an automatic balance. There are techniques to ensure balanced allocation to both the groups. These can be grouped according to the various stage of the trial. One way randomization can ensure a balanced base line characteristics is by stratifying the groups according to variables which are known to have prognostic significance (like age, gender, comorbidity status, etc.).[6] However, the number of strata needs to be reasonable. In the planning phase, a (permuted) block randomization ensures that equal numbers of individuals are randomized to the intervention(s) and control group. Once the study is on the roll, investigators could allocate treatment through minimization in order to ensure a balance.[7] This can be challenging since complete information should be available as the patients accrue over course of some time.

The second feature which makes the RCT robust is the elimination of bias. In scientific terms, bias is defined as an opinion or point of view without (objective) evidence to back it up.[8] Bias can distort the trial at the planning, analysis or conduct of the trial. It can introduce systematic errors, which can make the results questionable. There is a long tradition in RCT- research to tease out bias in order to make the investigation impartial and robust. Though a long-list of biases exist, discussion of which is beyond the scope of this write-up. It is important to bear in mind that bias at the design stage could mar the whole trial. A certain degree of distanced neutrality should be there when highlighting the clinical equipoise of the research question. Clinical investigators are liable to 'believe' in their intervention, introducing a bias at the design stage. This might be less of a problem in a non-inferiority trial, where an established intervention already exists and investigators only serve to measure the equivalence of new intervention with the gold-standard. However, investigator who happens to be a clinician is (also) invested in the outcome of newly designed intervention. The outcome of treatment is the sole focus for both the clinicians and clinical trial Investigators (Trialists). However, there is different form of investment from each individual. The former is keenly focused on the individual patient outcome while the latter is interested in generalizability of the findings to similar patient population. The trial outcome is something that should be free of bias in order to results to be credible.

Since science progresses through falsification of false evidence, eventually moving towards the truth, a preconceived notion of truth only serves to eclipse the reasoning-skill. Masking or blinding is one way of achieving the neutrality of observation. There are some circumstances in which it is extremely difficult, if not impossible, to construct an inert placebo. Ethical considerations also impede the use of Sham procedures or dummy patches. Some discourse on the trial end point and outcome

measure is also relevant when planning a trial. The outcome measure has to be quantifiable. It should also carry a clinically meaningful effect. The calculation of effect size is dependent on the response rate (or mortality) in the placebo group. The amount deemed to be significant in terms of clinical trial is a decision which investigators have to take at the very beginning. This estimation is always a trade-off between what is desirable and what is practical. Since time and resources are limited some deliberation should happen on the outcome.[9]In recent years, there is an increasing trend to look at the surrogate outcome(s) as a trial endpoint. This can come handy in terms of quantifying the final outcome measures. However, there has to be a meaningful correlation between the surrogate and final

outcome measures. A surrogate measure may yield a trial endpoint but its correlation with the final outcome needs to be looked in to keeping in view the natural history of the disease.[10] The development of an antibody may indicate immune response but may not alter the mortality rates in the long-run. The investigators should finalize the trial endpoint at the very beginning in consultation with all stake holders including a statistician. He/she might be able to guide the principle investigator on the binary versus continuous nature of the outcome, thereby planning the appropriate analysis.

Blinding or masking serves to reduce the selection bias and differential treatment of the trial participants. All attempts should be made to mask the patients, investigators and the assessors in the clinical trial. Administration of a placebo or inert substance in order to mask the administration of active comparator is standard practice in drug trials. In recent years papers have been published describing the methodology of double dummy technique in order to mask two different forms of drug delivery methods, i.e. oral versus injectable. In circumstances when blinding is not possible, like comparison of medical and surgical intervention, efforts should be made to have blinded assessments.[11]

An important pre-requisite to conduct of a trial is systematic review of evidence on the question of interest. This not only saves the cost but also sets the research question in the light of available evidence. [12] When combining the results of multiple trials in order to have a pooled estimate, biased trials will lead to an overestimation of treatment effect. This is more so in trials with small sample size, inadequate concealment of allocation sequence after randomization and disproportionate loss of follow-up and per protocol analysis as opposed to the intent-to-treat analysis. When a scatter diagram is plotted, it will display an inverted funnel. Classically, this visual display is seen as a measure of a publication bias. Absence of display dots (indicating individual studies) on the right hand side of the funnel indicates unpublished studies. They are expected to have insignificant results, deemed unpublishable by the authors and editors. Studies with significant treatment effects and small sample size, plotted on the middle to left side of the funnel, nevertheless might also be biased. Element of chance and random variation can also play a role in variable treatment effect; factors like variable adherence, investigators expertise and enthusiasm can also have a bearing on

the treatment estimate. True to the adage garbage-in, garbage-out-biased trial will lead to significant heterogeneity and inadequate pooling of result in meta-analysis. Another factor which could lead to biased estimate of treatment effect is the variable risk of the illness. Individuals with high initial risk are likely to respond better, with greater treatment effect than those with less risk to begin with.

Intuitively this also makes sense. Individuals with great symptoms at baseline and higher morbidity risk will show greater reduction in the absolute risk compared to asymptomatic individuals. Additionally, subgroup data also need to be stratified when pooling in the combined effect from multiple trials in order to avoid heterogeneity and have valid results.

Clinical trial stakeholders include the investigators, sponsor, ethics committees and the patients themselves. Safety of the patients is extremely important and cannot be overlooked. For this very reason, an informed consent is signed at the very start by the patient and the principal investigator. The study details are briefed by the investigator to the patient and consent is sorted. Investigator is liable to report any drug related adverse events to the ethics committee, sponsor and the relevant safety committees.

The sponsor closely follows the adverse drug events and investigator take appropriate pre-determined action as streamlined in protocol for the safety of the patient. It is important to note that it might not be ethically justifiable to withhold treatment from a group of patients, just for the sake of experiment, if an effective and reasonable intervention exists.

However, the definition of effective intervention is a matter of debate among the community of experts. A trial is only undertaken if there is equipoise in terms of efficacy of treatment 'A' over 'B'. A group of experts, scientists, ethicists and representatives of patients sit on an ethics review committee and debate over the scientific and ethical aspects of the trial. A trial is only undertaken if an independent ethics committee approves the conduct of the trial. This is supposed to ensure the safety of the patients enrolled in the trial as well as facilitation of the advancement of the science for general good of the society including the future patients.[13]

The governance of clinical trials is an important issue, with guidelines streamlining the processes. Clinical trials should be carried out in compliance with the Good Clinical Practice (GCP) Guidelines, which are international, ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects.[13] Compliance with GCP assures that the rights, safety, and well-being of the trial subjects are protected and that the clinical trial data are credible. GCP and other regulations on human research in drug development have now been formalized in many international and national guidelines and regulations. Adherence to the GCP Guidelines, constitution of Data Safety and Monitoring Board (DSMB) and Trial Steering Committee (TSC) are central to any sponsor led trial and investigating the medicinal product.[14]

All over the World, clinical trial research has taken a new importance given the advancement of science, development of new drugs, prevention programmes meant to combat the ever increasing burden of diseases. Renowned Universities in Pakistan are also establishing Clinical Trial Units in order to streamline the research investigating the efficacy of various interventions in disease prevention and management. It is also important to make a concerted effort to build capacity in the area of clinical trial research and teaching.

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# RANDOMIZATION

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Randomized Controlled Trial (RCT) is designed to study the effect of interventions in healthcare. A fundamental characteristic of an RCT is the decision about who is going to take what intervention (or arm /group of the trial) is made randomly. Randomization is seen as an attempt to align with the distribution of nature and reduce the element of bias embedded in the choice of the investigator. Improper randomization can manipulate results to show overestimated treatment effects. This can be as high as 40% (Schul, Grimes, et al).This is a matter of concern particularly in comparative, experimental studies. Selection of the comparison group(s) poses a challenge for trialists; they can be potentially different from each other and can render the researcher to instill a bias in the study during selection. Randomization becomes vital to ensure that individuals in both arms under study have an equal opportunity to receive any particular treatment. Randomization when done correctly ensures that the two groups are equal in characteristics which are known, and those which are unknown, and the only difference observed between two groups is due to the intervention alone.

Randomization serves two essential purposes; firstly randomization reduces selection bias which could creep in given the enthusiasm of the investigator, secondly, random allocation makes it more likely for the comparative groups to be balanced in baseline characteristics. These differences can be known or unknown. Relying on randomization generate similar, if not identical, groups. are recognized as **baseline imbalance** (Table 1). But as the sample size gets larger, it becomes closer to the natural distribution that preexists in the distribution pattern. In larger samples the groups have little difference among them at baseline, and if present, at all, are due to chance alone; henceforth, statistical methods can be applied to handle them.

*The analysis of trials assumes that only two reasons are responsible for outcome differences in two or more groups: either they are the result of imbalanced randomization or the difference is due to treatment intervention.*

The hypothesis testing offers the logic that if the difference is significantly great, and such imbalance is too large to occur by chance alone, then this difference must be attributable to the treatment intervention.

## Types of randomization:

Methods have been proposed to randomly allocate the subjects to either intervention or control group ranging from as simple as flipping a coin to as complex as covariate adaptive randomization. The coming section discuss these methods of random allocation. The shared hypothesis remains the same i.e. random assignment implies that it is not possible to predict in prior which arm a subject will be allocated to.

All types of randomization possess their own strengths and limitations that are important to take into consideration while choosing them for use in clinical trials.

## Simple randomization:

The basic randomization relies on one of the most simple and commonly used methods to choose i.e. tossing a coin. This is commonly called simple randomization. In a study with two arms treatment vs. placebo, sides of the coin (for example, heads for placebo and tails for Treatment) will assign the allocation arm for the subject which is also kept secret. A sealed envelope is used which patients are expected to take to the treatment center.

It is to note that previous assignments are not taken into consideration when allocating the next subject in the same way. Other convenient method of simple randomization could be assignment to treatment arm by choosing through shuffled cards (odd for placebo or even for treatment, or vice versa), spinning a wheel etc. In practice, a table of random numbers is also charted or computer software is used to generate list of random numbers.

*Randomization code* is the list that tells which subject will be given what treatment. In a random number table odd number can be used for treatment "A" while even number can be used for treatment "B" Simple randomization is the method that offers obvious advantages: it is simple, hard to predict and resonates with laws of nature, i.e. chance. Simple randomization can be used when overall sample size is large and there are no baseline prognostic factors which need to be balanced between two groups. It can causes imbalances in numbers assigned to each arm when sub-group prognostic factors have important role.

It entails risks or imbalance in characteristics of subjects involved when sample size is limited. In small size trials this can significantly reduce the precision of 'estimates of treatment difference' and therefore this type is usually recommended in sample sizes greater than 100.

**Table 2. Example of Simple Randomization**

| | |
|---|---|
| **1** | B |
| **2** | A |
| **3** | B |
| **4** | A |
| **5** | A |
| **6** | B |
| **7** | A |
| **8** | B |
| **9** | B |
| **10** | A |
| **11** | B |
| **12** | A |
| **13** | A |
| **14** | B |
| **15** | B |
| **16** | B |
| **17** | A |
| **18** | B |
| **19** | A |
| **20** | B |

**Table 3. Stratified randomization in Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE)**

| | Early Cohort | Early Cohort | Late Cohort | Late Cohort | Total |
|---|---|---|---|---|---|
| | Patients Without Tardive Dyskinesia | Patients With Tardive Dyskinesia | Patients Without Tardive Dyskinesia | Patients With Tardive Dyskinesia | |
| **Olanzapine** | 118 | 33 | 152 | 33 | 336 |
| **Quetiapine** | 116 | 34 | 154 | 33 | 337 |
| **Risperidone** | 127 | 33 | 148 | 33 | 341 |
| **Ziprasidone** | - a | -a | 153 | 32 | 185 |
| **Perphenazine** | 110 | -a | 151 | -a | 261 |

***a: precluded by study***

***Ref*: Kraemer HC, Glick ID, Klein DF. Clinical trials design lessons from the CATIE study. *Am J Psychiatry*. 2009;166(11):1222-1228. doi:10.1176/appi.ajp.2009.08121809**

## Example:

In a trial of Treatment (A) and Placebo (B) a total sample size of 20 subjects is allocated to either arm randomly and results

| Table 1. Example of baseline characteristics of two arms | | |
|---|---|---|
| | **Methotrexate (n=45) Mean** | **Placebo (n=47) Mean** |
| **Age** (years) | 24.8 | 26.6 |
| **Education** (years) | 5.7 | 7.0 |
| **Clinical global impression** (CGI) | 4.5 | 4.4 |
| **PANSS** (subscale score) | | |
| Positive symptoms | 18 | 15.7 |
| Negative symptoms | 16.4 | 15.0 |
| General psychopathology | 30.4 | 28.4 |
| Total score | 64.8 | 59.0 |
| | **N** | **N** |
| **Sex** | | |
| Male | 35 | 32 |
| Female | 10 | 15 |
| **Marital status** | | |
| Single | 29 | 37 |
| Married | 15 | 9 |
| Separated | 0 | 1 |
| Divorced | 1 | 0 |
| **Diagnosis of SCID** | | |
| Paranoid type | 32 | 28 |
| Disorganized type | 2 | 6 |
| Undifferentiated type | 11 | 9 |
| Residual type | | 3 |
| Schizoaffective disorder | | 1 |
| ***Ref:*** **Chaudhry et al. Translational Psychiatry (2020)10:415)** | | |

in unequal arms of 9 (A) and 11 (B) subjects each (Table 2)

## Stratified randomization:

Stratification is a suitable method to maintain the balance between two groups with significant baseline differences (covariates). It keeps the randomization uniform and valid throughout the study. It is done by identifying and stratifying the groups for pre-determined (prognostic) factors and then allocating the treatment across these strata.

The information on baseline characteristics comes from previous literature and studies looking at the similar population. The combinations of covariates are generated, when there are multiple factors, and then each subject is allotted the treatment. Care has to be taken that equal number of treatment options (A or B) are assigned across the strata. Simple randomization can be

| Table 4. Example Of Block Randomization with 6 blocks each size of 4 | | | |
|---|---|---|---|
| **Block** | **Permutation** | **Patient** | **Study Arm** |
| 1 | 4 | 1<br>2<br>3<br>4 | Placebo<br>Minocycline<br>Placebo<br>Minocycline |
| 2 | 1 | 5<br>6<br>7<br>8 | Placebo<br>Placebo<br>Minocycline<br>Minocycline |
| 3 | 6 | 9<br>10<br>11<br>12 | Placebo<br>Minocycline<br>Minocycline<br>Placebo |
| 4 | 3 | 13<br>14<br>15<br>16 | Minocycline<br>Placebo<br>Minocycline<br>Placebo |
| 5 | 5 | 17<br>18<br>19<br>20 | Minocycline<br>Placebo<br>Placebo<br>Minocycline |
| 6 | 2 | 21<br>22<br>23<br>24 | Minocycline<br>Minocycline<br>Placebo<br>Placebo |

carried out within each stratum to allocate the treatment across the two arm of the study.
The baseline imbalances are reduced through the stratification; however, the power of the study is reduced since each group is assigned less and less subjects. It is better to adjust for the covariates rather than correcting them afterwards through statistical methods. Stratified randomization can become challenging in larger trials which can have greater number of covariates that are needed to be controlled.

A process called minimization is used, which ensures near similar allocation sequence, i.e. treatment is allocated to keep the difference of allocation (between treatment A and B) to minimal. Stratified randomization requires identification of the baseline charact erstics of the subjects before assignment to treatment groups. The baseline data is generally collected after informed consent and before assignment to treatment groups. For stratified randomization, baseline characteristics to be stratified must be available for all subjects enrolled in the study which may offer some practical difficulties.

**Table 5. Example of Minimization**

| | | Methotrexate | Placebo |
|---|---|---|---|
| **Gender** | Male | 35 | 32 |
| | Female | 10 | 15 |
| **Diagnosis of SCID - Schizophrenia** | Paranoid type | 32 | 28 |
| | Disorganized type | 2 | 6 |
| | Undifferentiated type | 11 | 9 |

## Example:

In a landmark study exploring the treatment options for schizophrenia, CATIE Trial (Table.3), a sample of 1,493 patients with schizophrenia were recruited at 57 sites. The trial group was stratified into four strata: by presence or absence of tardive dyskinesia and by cohort i.e. those enrolled before inclusion of ziprasidone (early) and those enrolled after that (late).

Then each stratum was assigned five different antipsychotics namely olanzapine, quetiapine, ziprasidone, risperidone and perphenazine. This was done to ensure balance in the stratified factors at baseline.

## Block Randomization:

Block randomization allows random allocation of subjects while balancing the number of subjects in all arms. *Blocks are subsets of subjects* that work as assignment units to equal the distribution of sample size to both arms of the study. Block size is varied in that treatment allocation is hard to predict. Block is determined by the trial team in advance and should be a multiple of the arms of study i.e. for a two arm study block size will be 2, 4, 6 or 8 etc. Block design method comprises following steps:

- Choose the size of block.
- Calculate the numbers of blocks that are required to include all the subjects of the study.
- Make a list of all possible permutations (combinations) of treatments in a block
- Randomly assign the order to the blocks by generating randomization code for their selection.

Block randomization requires the trial to run its full course. If the trial has to be stopped early for any reason, there would be imbalance in treatment arms. In a sample size of 60, 10 blocks of 6 subjects can be used and premature results or halt can coincide with the end of a block resulting in almost equal size of each arm. Selection bias can arise from block randomization. The treatment arm becomes predictable especially for the last subject of the sequence.

For example, in a sequence of four, every fourth subject can be predicted and also third in case of AABB or BBAA sequences. This is avoided by varying the size of the block. This

predictability occurs if the allocation sequence is not masked or the researcher is aware of previous allocations. The best way to avoid this selection bias is to mask the treatment allocation and to blind the assignment to the properties of the blocks: their orders and their respective sizes. For the later purpose blocks of varying sizes such as 2, 4 ,6, etc are used in random sequence.

## Example:

In a trial comparing efficacy of minocycline vs placebo (Table 4) in patients with recent onset psychoses, a sample size of 24 patients was obtained. The block size of 4 was used in this two arm trial (as 2 will become too predictable and 6 too large for the given sample size). To cover 24 patients with a block size of 4 each, a total of 6 blocks were generated. A block size of 4 means that after every fourth subject, the number of patients in each arm are equal. Therefore each block will have two patients of each treatment arm (placebo arm and minocycline arm). The sequencing of both treatment arms (i.e. 2 placebo and 2 minocycline) in each block can have six possible forms, known as **permutations**, as given in table 4. Finally a random number list from 1 to 6 for these six permutations can be produced as randomization codes.

## Minimization:

For tighter control of covariates, minimization is used. Minimization is one of the adaptive randomization methods. It is generally done through a computer programme. The fundamental principle of minimization is allocation of subjects in a way that it minimizes the baseline imbalances of prognostic factors as the subjects enter the study.

- The first subject is randomly allocated to a group.
- The subsequent subjects are allocated to group through randomization that would minimize the imbalance.

The minimization largely decreases the baseline imbalances between groups but it does so at the price of loss of true randomization since the subjects are allocated to arms not by mere chance.

## Example:

In a trial of efficacy of Methotrexate vs Placebo in psychosis, distribution of two baseline characteristics was as given in Table 5. Assume that the next patient who comes up is male and has been diagnosed as paranoid type of schizophrenia. The patients with similar characteristics in each arm are calculated by summing up data in each row as follows:

Sum for Methotrexate = 35 + 32 =67
Sum for Placebo = 32 + 28 =60

The allocation in minimization follows the arm with the smallest marginal total, in above scenario that is placebo. The patient with these characteristics will be allocated to placebo group. If both arms' sum turn out to be same, then simple randomization will be used to allocate the group.

## Allocation concealment:

Allocation concealment refers to concealing the allocation sequence from the person who is assigning the groups to the subjects .The participants remains unaware of the treatment until assignments are done. Allocation concealment controls *selection bias* therefore securing the process of randomization. Unconsciously or even consciously the knowledge of subjects and intervention arm can interfere with the researcher's decision. For example, trialist can assign an individual with good prognosis to intervention arm rather than TAU (Treatment As Usual) based on his enthusiasm for the new intervention.

Allocation concealment is different from blinding. It protects against selection bias in contrast to observational bias protected by blinding.

The concealment of allocation can be carried out through conventional methods such as using an opaque envelop that carries either of the arm's intervention.

Other methods are more reliable such as using distant randomization (Table 6) in which the assignments are carried out totally away from the researchers involved directly.

**Example of Allocation Concealment:**

*"Each participant will be assigned a unique study patient identification number once they have given informed consent and eligibility has been confirmed. The central trial pharmacist will prepare a 12-week package of treatment bearing the patient's name and ID number and send it to the site pharmacy. Thus, the site pharmacy will not know the treatment allocated of the patient. A study information leaflet will be given to the participant, explaining that they are in a clinical trial and that in addition to TAU they are taking a placebo or simvastatin. This leaflet will also have the name of the local principal investigator. Allocation will be masked from study investigators and co investigators until participants have completed all follow-ups and the database is cleaned and locked. The trial pharmacist at the central pharmacy will keep the drug codes".*

Ref: Husain Husain MI, Chaudhry IB, Khoso AB, et al. Adjunctive simvastatin for treatment-resistant depression: study protocol of a 12-week randomised controlled trial. BJPsych Open. 2019;5(1):e13. doi:10.1192/bjo.2018.8

# BLINDING IN CLINICAL TRIALS

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In any clinical trial bias is one of the main concerns, especially in determining treatment effect. **Bias** may be defined as unconscious preference, favor or inclination of one outcome over another or a systematic error. In essence it is a "difference between the true value and that actually obtained due to all causes other than sampling variability". It's naturally expected for investigators to be excited about a new intervention which might have a promise or patients to be optimistic since existing intervention might not be effective or may have serious adverse events. Bias can occur at various points in a clinical trial, from the initial design to data analysis, interpretation and reporting. One solution to help eliminate bias is to keep the participants and the investigators blinded, or masked, to the identity of the assigned intervention. Other aspects of a trial conduct, including the assessment, classification and evaluation of the response variables should also be blinded when feasible. A large sample size, alone, does not lead to reduced bias.

**The first clinical trial in modern times which applied the principle of blinding was published in 1931 by Amberson et al. This trial was in all likelihood also the first trial that employed a form of random assignment of participants to the study groups. A survey of 91 internal medicine physicians in Canada (2001) showed that 75% knew the definition of single blind and approximately 40% understood the proper definition of double-blinding. Among 66 single-blind trials, the investigators were asked who was blinded. Twenty-six said the patients, 22 the outcome assessors and 16 the data analysts/investigators were blinded in a trial. Viergever and Ghersi also reviewed to what extent information of blinding was part of registered records of clinical trials and then concluded that this information was often not provided or was of poor quality in trial publications. The authors concluded that the term double-blind was found to be common despite the lack of understanding on its exact meaning.**

## UNBLINDED STUDY DESIGN:

In an unblinded or open trial, **both the participants and the investigators know** to which intervention the participant has been assigned. Some kinds of trials are primarily conducted in this manner and those include most surgical procedures, comparisons of devices and medical treatment, changes in lifestyle (e.g. eating habits, exercise, cigarette smoking) or learning techniques when masking is hard to implement or unethical given the risks entailed in the investigation. An unblinded study seems appealing for two reasons 1) investigators are more comfortable making decisions, such as whether or not to continue a participant on the assigned study medication given the severity of the illness or clinical preference based on existing guidelines 2) often they are simpler to execute than other studies. The usual drug trial may be easier to design and carry out, and as a result, less expensive, if blinding was not an issue. Also, it has been argued that it accurately reflects routine clinical practice. However, an unblinded trial need not be simple. For example, trials that attempt to induce lifestyle changes and test drug interventions at the same time can be fairly complex. For e.g. the Women's Health Initiative which had three distinct interventions: hormone replacement therapy, calcium and vitamin D supplementation and an unblinded dietary intervention. The main disadvantage of an unblinded trial is the strong possibility of a bias. Participants reporting of symptoms and side effects and prescription of concomitant or compensatory treatment are all susceptible to bias. Participants when joining a trial have expectations about the beneficial effects of the new intervention and they may become dissatisfied and drop-out of the trial in large numbers if they are not on the perceivable new or experimental intervention. The benefit of blinding in trials of a short intervention (such as treatment with a fibrinolytic agent for acute myocardial infarction) where differential drop-out is unlikely, and with an outcome (like all-cause mortality) that is not subject to ascertainment bias can be debated. However, even in these trials assessment of other adverse events will be protected from bias with blinding.

**A trial of the possible benefits of ascorbic acid (vitamin C) in the common cold was designed as a double-blind study. However, it soon became apparent that many of the participants, most of whom were medical staff, discovered mainly by tasting whether they were on ascorbic acid or placebo. As more participants became aware of their medication's identity, the dropout rate in the placebo group increased. Since evaluation of severity and duration of cold (flu) depended on the participants' reporting of their symptoms, this unblinding was important. Among those participants who claimed not to know the identity of the treatment at the end of the trial, ascorbic acid showed no benefit over placebo. In contrast, among participants who knew or guessed what they were on, ascorbic acid did better than placebo. Therefore, preconceived notions about**

**the benefit of a treatment, coupled with a subjective response variable, may have yielded biased reporting.**

The investigators' willingness to share this experience provided us with a nice illustration of the importance of maintaining blinding.

## SINGLE BLINDING:

The established definition of a single-blind study is that **only the participants are unaware of which intervention they are receiving.** The advantages of this design are similar to those of an unblinded study—it is simpler to carry out than a double-blind design, and knowledge of the intervention may help the investigators use their best judgment for the participants. The investigator avoids biased participant reporting, but he or she can affect the administration of non-study therapy, data collection, and data assessment.

**For example, a single-blind study reported benefits from zinc administration in a group of people with taste disorders. Because of the possibility of bias in a study using a response variable as subjective and hard to measure as taste, the study was repeated, using a type of crossover, double-blind design. This second study showed that zinc, when compared with placebo, did not relieve the taste disorders of the study group. The extent of the blinding of the participants did not change; therefore, probably, knowledge of the drug identity by the investigator was important.**

Both unblinded and single-blind trials are vulnerable to a source of potential bias by the investigators. This relates to group differences in compensatory and concomitant treatment.

Investigators may feel that the control group is not being given the same opportunity as the intervention group and may prescribe additional treatment as "compensation." This may be in the form of advice or therapy.

**For example, several studies have attempted blood pressure lowering as either the sole intervention, or as part of a broader effort. In general, the investigators would make an intensive effort to persuade participants in the intervention group to take their study medication. To persuade successfully the investigators themselves had to be convinced that blood pressure reduction was likely beneficial. When they were seeing participants who had been assigned to the control group, this conviction was difficult to suppress. Therefore, participants in the control group were likely to have been instructed about non-pharmacological ways by which to lower their blood pressure or other preventive treatments.**

Working against this is the fact that investigators typically prefer to be associated with a study that gives positive findings. Favorable results published in a reputable journal are likely to lead to more invitations to present the findings at scientific meetings and can also support academic promotions. Investigators may, therefore, subconsciously favor the intervention group when they deal with participants, collect data, and assess and interpret results, although this may perhaps be less of an

issue in multicenter trials.

Concomitant treatment means any non-study therapy administered to participants during a trial. If such treatment is going to influence the outcome variable, this needs to be considered when determining sample size. More important is the bias that can be introduced if concomitant treatment is applied in unequal measures in the two groups. In order to have bias in the outcome of a trial, concomitant treatment must be effective, and used in a high proportion of the participants. If this is the case, bias is a possibility which may occur in either direction, depending on if the concomitant treatment is preferentially used in the control, or in the intervention group. It is usually difficult to determine the direction and magnitude of such bias in advance or its impact after it has occurred.

## DOUBLE BLINDING:

In a double-blind study, **neither the participants nor the investigators or more specifically the team of investigators responsible for following the participants, data collection, and outcomes assessment should know the identity of the intervention.** Such designs are commonly restricted to trials of drugs or biological products. The main benefit of a double-blind study is that the risk of bias is reduced. Preconceived notions of the investigators will be less important, because they will not know which intervention a particular participant is receiving. Any effect of their actions, therefore, would theoretically occur in equal measures in the intervention and control groups. The possibility of bias can never be completely eliminated.

However, a well-designed and properly run double-blind study can minimize bias. As in the example of the trial of zinc and taste impairment, double-blind studies have at times led to results that differ from unblinded or single blind studies. Such cases illustrate the role of bias as a factor in clinical trials.

**In one trial, an unblinded pharmacist or physician adjusted the warfarin doses according to an algorithm for maintaining the International Normalized Ratio (INR), within a pre-specified range but also adjusted the placebo doses randomly. The authors concluded that "placebo warfarin dose adjustment dose schedules can protect blinding adequately" for participants and investigators and recommended their use for future trials of warfarin.**

In a double-blind trial certain functions that were accomplished by the investigators in unblinded or single-blind studies might sometimes be taken over by others in order to maintain the blinding. These functions are participant care if it is important for the patient care to know the intervention, collection of efficacy and safety data that might disclose the nature of the intervention, and assessment and monitoring of treatment response. Typically, an external body needs to monitor the data for toxicity and benefit, especially in long-term trials. A person other than the investigator who sees the participants needs to be responsible for assigning the interventions to the participants. Treatments which require continuous dose adjustment, such as warfarin, are difficult to blind, but it can be accomplished.

## TRIPLE BLINDING:

A triple-blind study is an extension of the double-blind design; **the committee which monitors the response variables is not told the identity of the groups.** The committee is just given data for groups 1 and 2. A trial statistician is given this task which is built into the charter of the interim analysis or final report while constituting the Data Monitoring Committee (DMC). A triple-blind study has the advantage of allowing the monitoring committee to evaluate the outcome variable results more objectively.

This assumes that appraisal of efficacy and adverse effects, as well as requests for special analyses, may be biased if group identity is known.

Although, in a trial where the monitoring committee has an ethical responsibility to ensure participant safety, such a design is counterproductive. When tasked with the safety-monitoring role, the committee cannot carry out its responsibility to minimize harm to the participants, since monitoring is often guided by the constellation of trends and their directions. However, even if the committee could perform its role

adequately while being kept blinded, many investigators would be reluctant to participate in such a study.

In most cases the monitoring committee only looks at the group data and can rarely make informed judgments about individuals, howover,the investigators still rely on the committee to protect their study participants. This may not be a very rational approach due to the fact that, by the time many monitoring committees receive data, often any emergency situation has long occurred. Nevertheless, the discomfort many investigators feel about participating in double-blind studies is amplified when the data monitoring committee is kept blinded. However, this is an essential component which ensures transparency of results and integrity of the trial data. Increasingly FDA has made it mandatory to have a DMC chartered a trial review for a licensing requirement.

Lastly, people tend not to accept beneficial outcomes unless a statistically significant difference has been achieved. Although it is rare that investigators would want to continue a study in order to achieve a clearly significant difference in an adverse direction i.e. until the intervention is statistically significantly worse or more harmful than the control. Owing to this, many monitoring committees demand to know which study groups are on which intervention. A triple-blind study can be conducted ethically if the monitoring committee asks itself, at each meeting, whether the direction of observed trends matters. If it does not matter, then the triple-blind can be maintained, at least for the time being.

## PROTECTING THE DOUBLE BLIND DESIGN:

It must be ensured that the investigators remain blinded and that any data which may endanger blinding be kept away from them during the study. An **effective monitoring scheme** of the data must be set up, and emergency unblinding procedures must be established. These requirements pose their own problems and can increase the cost of a study. Page and Persch discussed strategies for blinding both health care providers and data collectors. The latter were to be different from those providing medical care for the participants.

Protecting the double-blind can be problematic in active-control trials. These are trials comparing active interventions. The side effect patterns for the drugs being compared can be different.

**When the selective serotonin receptor inhibitors (SSRIs) were first introduced they were compared to tricyclic antidepressants (TCAs). The TCAs are anticholinergic and commonly cause dryness of mouth, blurred vision and tachycardia. The occurrence of these side effects unblinded the treatment in a large number of participants in 20 comparative trials.**

Participants generally want to be on the "best" intervention. In a clinical drug trial, the "best" intervention usually is presumed to be the new one; in the case of a placebo-control trial it is presumed to be the active medication. Investigators may also be curious about a drug's identity. Due to these reasons, consciously or subconsciously, both participants and investigators may try to unblind the medication.

Unblinding can be done deliberately by going so far as to have the drug analyzed, or in a less purposeful manner by "accidentally" breaking open capsules, holding pills up to the light, carefully testing them, or by taking any of numerous other actions. The less purposeful form of unblinding is more common. In one study a participant reported that the previous capsules use to float in the water closet (WC) of a lavatory as opposed to the new one in a switch over trial! It is highly recommend that the assessment of the outcomes of the trial be as objective as can be possible. This means that the person at the clinic making these assessments – assessor - be blinded.

## OFFICIAL UNBLINDING:

A countermeasure should be developed to quickly break the blind for any individual participant at any time, should it be in his best interest. Such systems include having labels on file in the hospital pharmacy or other accessible locations. To avoid needless breaking of the code, someone other than the investigator could hold a list that reveals the identity of each drug code, or each study drug bottle label might have a sealed tear-off portion that would be filed in the pharmacy or with the participant's records.

In an emergency, the seal could be broken and the identity of the drug revealed. **Official breaking of the blind** may be necessary. There are always going to be situations that may require full disclosures, especially in long-term studies. The study medication requires tapering the dosage or children may get a hold of study drug pills and swallow them. In an emergency situation, knowing that a participant is or is not on the active drug would indicate whether tapering is needed. Generally, most emergencies are handled by withdrawing the medication without breaking the blind.

When the treating physician is different from the investigator, a third party can obtain the blinded information from the pharmacy and relate the information to the treating physician, and the participant and the study investigator need not be unblinded. Knowledge of the identity of the study intervention rarely influences emergency care of the participant. This information is important for treating physicians to know since it can help reduce the frequency of unnecessary unblinding. When unblinding does occur, the investigator should review and report the circumstances which led to it to the **Trial Executive Committee (TEC)** which has the responsibility of initiating a dialogue with the sponsor. This should also be reported in the results paper as a matter of full disclosure (if results are imparted). In summary, double-blind trials require meticulous planning and constant monitoring so as to ensure that the blind is maintained and participant safety is not threatened.

# CONTROL GROUP IN CLINICAL TRIALS

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A well raised research question is central to evidence based medicine (EBM). In this regard, the PICO model (Population, Intervention, Control and Outcome) provides a suitable framework for systematic exploration of the evidence. In a clinical trial, 'C' in PICO stands for Control, Comparison or Comparator and constitutes one of the integral features of a randomized control trial.

Comparison or controls are groups against which an intervention is experimented in a standard randomized controlled trial (RCT). The purpose of control group is to allow the researcher determine that the observed results are truly caused by the intervention or they are the outcome of other factors such as natural disease progression, expectations of the subjects or observers or other treatments etc. Control group gives information on what would have happened to participants if they had not been provided with the experimental treatment or if they had received different treatment. The ever changing nature of diseases, population characteristics and environment makes it almost impossible to compare the treatment results with its known outcome without treatment. Therefore in RCTs, Control group is essentially required for comparison to generate highest form of evidence.

In a randomized controlled trial control group can take many forms as given in table 1. The choice of a comparator group is a critical step in designing an RCT. While selecting a control group, investigators look at certain contextual details; they look for what are the already effective treatments available? What are the evidence to support the type of control group selected? Are there any serious ethical considerations? It is important to carefully select a control group for an RCT since it can substantially affect the conclusions drawn from the trial and raise concerns about its ethical acceptance.

Among the characteristics of control group the most significant is its similarity with intervention group. The control group should closely resemble with treatment group whenever applicable. This implies that they must share all baselines variables and on treatment variables with the exception of intervention which is under study. Inability to do this results in bias and the treatment effect would not be interpreted with its true value. Steps that can reduce these biases include randomization and blinding. This will ensure to some extent that both groups are similar at the beginning of study and are dealt equally throughout the study.

The best control group would be the one that is cleanest to compare with i.e. a group which gets the inactive treatment (no active treatment or placebo ) that can be blinded to appear similar to tested treatment; and there are no co-interventions either, that carry a risk to impact the results.

Placebo Controlled Trials: Placebo in an RCT is an agent that resembles as closely as possible to the experimental treatment but do not contain the active ingredient of that treatment that is responsible for its effect. Placebo originates from a Latin word translating to 'I will please' .It highlights the fact that it is considered as an 'epithet assumed for any medicine that provides more pleasure than actually benefitting the patient'. History of placebo effect can be traced back to civilization of human beings. The placebo effect became popular after WWII when Beecher demonstrated placebo effect on war soldiers by giving them normal saline injectable as placebo for analgesics and other treatment. Placebo effect has a bio psychosocial basis. Placebo Effect is usually but not always positive and is produced due to power of suggestion .It is attributed to the expectation that a treatment will have an impact.

Placebos are carefully designed to match the experimental treatment in physical characteristics for instance the color, shape, odor and taste etc. Placebo controlled studies are beneficial in numerous ways. They provide robust evidence about the tested treatment since they are randomized and double blinded i.e. placebo and treatment are randomly assigned and both the researcher and patients are unaware of whether they are assigned to placebo or treatment group. They can also report for any adverse event directly arising from the intervention and differentiate them from effects of the disease itself or other interferences.

Placebo do not merely control for placebo effect (the psychological effect of treatment causing benefit) of the intervention. Placebo minimizes bias by randomization and blinding along with the addition of a group with inert treatment; hence it controls for all the factors influencing the outcome other than one factor i.e. pharmacological effect of the treatment. Therefore, they have an ability to demonstrate 'Absolute efficacy' meaning that the difference in groups is purely attributa-

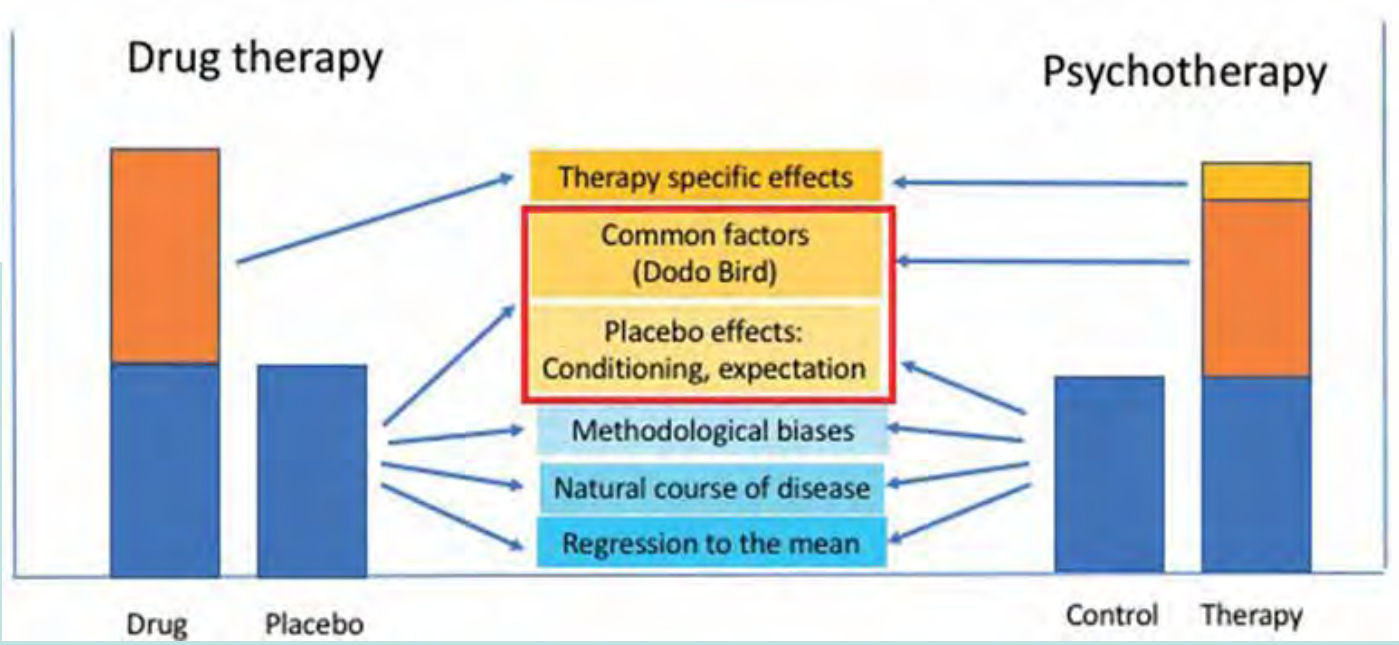

ble to pharmacological effects of intervention and this difference can be safely interpreted without reference to external sources.

There are some well-known ethical and practical concerns related to placebo controlled trials. A placebo is not acceptable as a control in conditions where there is a treatment known to be effective in preventing any worse outcome including irreversible harm or mortality. The guidelines presented by Office for Human Research Protection (OHRP) states, 'Investigators may opt for placebo as control in clinical trials when there is lack of known or available (e.g. FDA approved) alternative treatment that subjects can tolerate.' Therefore, the pre requisites for placebo use must include a positive risk benefit analysis and the fully informed consent from the participants about what placebo is and what are the risks involved.

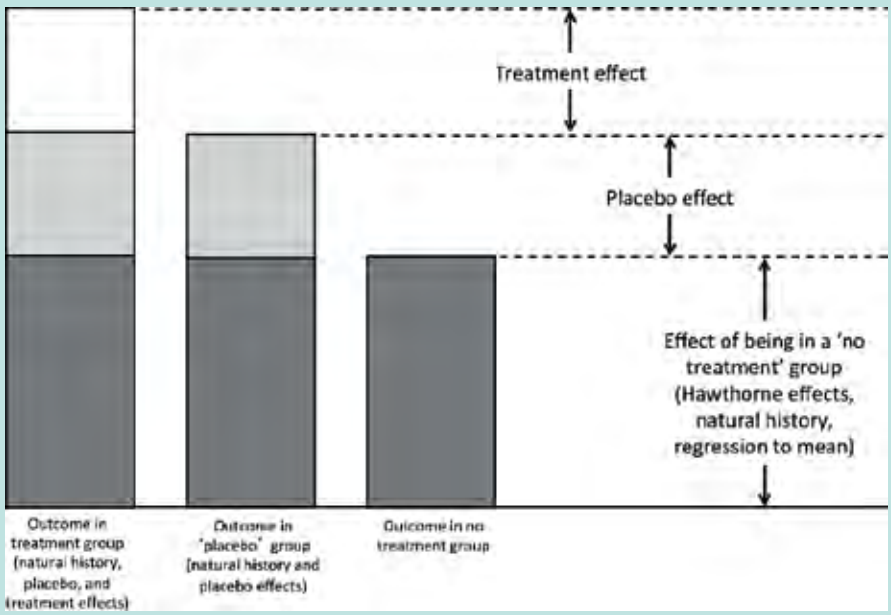
Active Control Trials: In studies where ethical principles do not allow to withhold, delay or deliver sub optimally effective treatment, a known effective treatment called active treatment is used as control. The experimental treatment is compared against the well-established treatment. When this comparison is done to establish that new treatment is better than the one against which it is compared, it is called a 'superiority trial'. If the purpose is to show that new treatment is as effective as the standard treatment it is labelled as 'equivalent trials'. When the trial attempts to show that the new treatment is not less effective than the standard treatment by more than a specified amount (known as margin), it is known as a 'non inferiority trial'.

In superiority, non-inferiority and equivalence trials, comparative efficacy is the aim of the study. Such designs h have strength to differentiate effective treatment from none or less effective one. This ability of clinical trials is known as Sensitivity Assay. For fair comparisons, the conditions of the trial should not unduly favor any one of two comparative treatments. The following aspects of clinical trial have propensity to favor one treatment over other and need to be kept in check while planning a trial.
Patient population: If patients chosen are poor responders to control treatment their response towards experimental treatment would be biased in its favor. This evidence is not completely rejected since it can provide evidence of efficacy in the studied population. Moreover it can lead to a new possibility of effective treatment in those who are poor or non-responders to conventional treatment. However, these results cannot be generalized to all untreated patient population.

Dose: Consideration should be given to dose regimens for both active and control treatments. The results can be biased if a drug is used in too low dosages thus appears to be ineffective or a less well tolerated drug is used in higher dosages raising false alarm for its safety or tolerability.




Endpoints: The endpoint in clinical trial is the outcome of interest. The chosen endpoint can unfairly favor one treatment over another if different modalities or classes of treatments are used. For example CBT responds in duration longer than an SSRI and an endpoint of shorter duration would give biased results towards SSRI.




The other descriptive terms for active control group have slight differences among them. TAU - Treatment As Usual; Usual Care; Routine or Standard Care are synonymous terms used for routinely provided treatment for patients which is then used as control treatment to compare new intervention. Gold Standard is the best treatment available which has already been proven effective. It is used as control to establish efficacy of newer treatment. It is now more common to use more than one category of control group. For example a placebo and an active treatment both are used against an experimental treatment. In such case, the placebo can serve as an internal control for the active treatment. In certain circumstances it is not possible to conduct a controlled clinical trial and an uncontrolled clinical trial is then carried out. It is reserved for conditions that have poor prognosis without intervention and there are no acceptable treatments available for that illnesses.

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Table 1. **Comparative (Control) Groups in a Randomized Controlled Trial**

| Control group | Description | Example | Treatment Group TG vs Control Group CG |
|---|---|---|---|
| **No Treatment** | No intervention is provided to participants in control | *A Randomized Trial of Dialectical Behavior Therapy Versus General Psychiatric Management for Borderline Personality Disorder* | TG = Dialectical Behavior Therapy CG = General Psychiatric Management |
| **Usual Care Treatment As Usual TAU Routine Care** | Treatment that is routinely provided at places from where recruitment is carried out of the participants | *Music therapy as an adjunct to standard treatment for obsessive compulsive disorder and co-morbid anxiety and depression: A randomized clinical trial* | TG = Music therapy CG = standard treatment |
| **Standardized Care Optimized Care** | If standard of care (SOC) exists but not practiced in the recruitment setup, the treatment being provided can be optimized for RCT to bring it near to SOC | *Delivery of Evidence-Based Treatment for Multiple Anxiety Disorders in Primary Care :A Randomized Controlled Trial* | TG = Coordinated Anxiety Learning and Management(CALM) CG = Optimized Usual care |
| **Standard of care Gold standard** | Treatments that are established as most effective acceptable for outcome of interest. No clear definition exists ; includes best treatment accepted by most experts , guidelines and protocols | *ELEctroconvulsive therapy (ECT) vs. Ketamine in patients with Treatment-resistant Depression: The ELEKT-D study A non Inferiority trial* | TG = Ketamine CG = Electroconvulsive therapy (ECT) |
| **Placebo Sham** | An intervention that resembles the experimental treatment but lacks its active agent | *Risperidone for psychosis of Alzheimer's disease and mixed dementia: results of a double-blind, placebo-controlled trial* | TG = Risperidone CG = Placebo |
| **Component** | Intervention which is similar to the experimental treatment except for its one or more components | *CBT for depression; a pilot RCT for comparing mobile phone vs computer* | TG = CBT mobile phone CG = CBT computer |
| **Dosage** | Intervention which is similar to the experimental treatment except for dosages such as amount of medicine, frequency or duration of treatment | *A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities* | TG = RUL ECT 50%, 150%, or 500% above the seizure threshold CG = BL ECT 150% above the seizure threshold |

# CLINICAL TRIALS
## PHASE I TO IV

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A clinical trial is a study that prospectively compares the value of intervention (s) versus a control in human beings. A clinical trial is prospective, instead retrospective, experiment. Study participants are followed forward in time to test one intervention against the other at a basic level. There is no need for all of them to be followed from an identical calendar date, rather this will occur rarely. Every participant must however, be followed from a well-defined point in time, which is then known as baseline for that person in the study to a defined end-point. A Clinical Trial must employ at least one or more intervention techniques. These may be single or combinations of diagnostic, preventive, or therapeutic drugs, procedures, or educational approaches. Intervention techniques should be applied to participants in a standard fashion in an effort to change some outcome.

Early phase studies may be controlled or uncontrolled. Common terminology refers to phase I and phase II trials, because they are sometimes uncontrolled, however they are also called clinical studies. A trial, using the definition given above, contains a control group against which the intervention group is compared. At baseline level, the control group must be similar enough in relevant respects to the intervention group so that differences in outcome can reasonably be attributed to the intervention. Unlike in animal studies, clinical trials cannot have the investigator dictate what an individual should do. He can at best, strongly encourage participants to avoid certain medications or procedures which may hinder the trial. Since it is impossible to have "pure" intervention and control groups, an investigator would have difficulty in comparing the interventions, but only intervention strategies.

Strategies refer to attempts at getting all participants to adhere, to the best of their ability, to their originally assigned intervention. When planning a trial, the investigator should recognize the difficulties inherent in studies with human subjects and attempt to estimate and gauge the risk of participants' failure to adhere strictly to the protocol.

**The ideal Clinical Trial is one in which there is randomization and double-blinding. The trials can be of explanatory/efficacy type or the pragmatic/effectiveness type.**

Traditionally, the trial phases for pharmacological agents have been divided into 4 steps: Phase I, Phase II, Phase III, and Phase IV. Here we can also demarcate them as Early Phase studies (Phase I and Phase II) and Late Phase studies (Phase III/IV).

### PHASE I:

Even though useful pre-clinical information may be obtained from in vitro studies or animal models, early data must also be obtained from humans. People who participate in phase I studies are healthy volunteers, but may be patients who have failed to improve on the existing standard therapies. Phase I studies attempt to find out the tolerability and characterize pharmacokinetics as well as pharmacodynamics. They focus on finding out the bioavailability and body compartment distribution of the drug and metabolites. **They also provide preliminary assessment of drug activity. One of the first steps in evaluating drugs is to estimate how large a dose can be given before unacceptable toxicity is experienced by patients. This is usually referred to as the maximally tolerated dose.**
Bayesian approaches that involve methods employing continual reassessment and escalation with overdose control. They involve the specification of the investigators' prior opinions about the drug's dose-toxicity profile, which is then used to select the starting dose, and escalation rules.

**The most common Bayesian phase I design is called the continual reassessment method, in which the starting dose is set to the prior estimate of the maximally tolerated dose. After the first cohort of participants (typically of size 1, 2, or 3, though other numbers are possible), the estimate is updated and the next participant(s) assigned to that estimate. The process is repeated until a pre specified number of participants have been assigned. The dose at which a hypothetical additional participant would be assigned constitutes the final estimate of the maximally tolerated dose.**

### PHASE II:

Once a dose or range of doses is determined, the next goal is to evaluate whether the drug has any biological activity or effect. The comparison may consist of a concurrent control group, historical controls, or pre-treatment status versus post

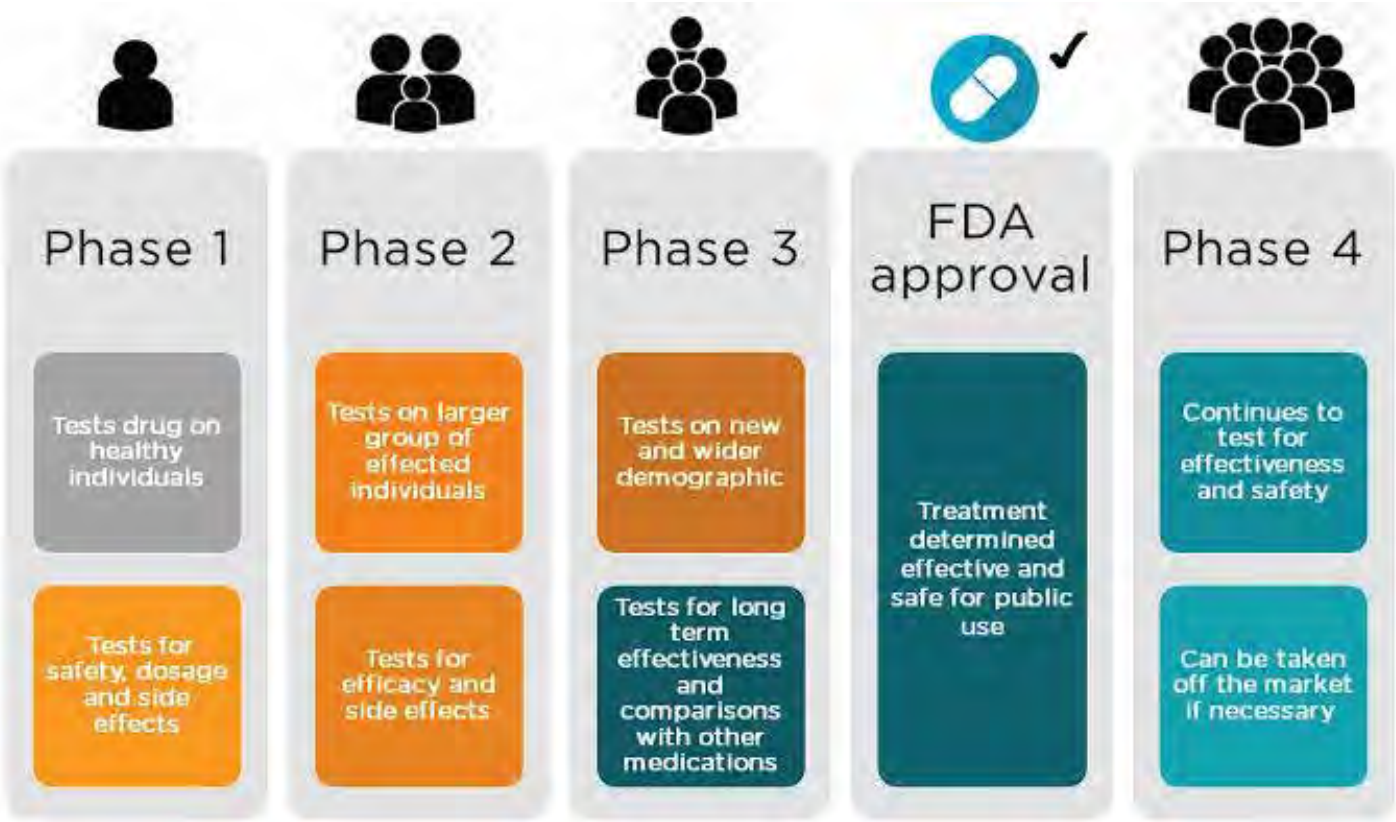
treatment status. Commonly, phase II studies are performed to make a decision as to whether to further develop a new drug or device. Hence, the purpose is to give an estimate of the probability of success in phase III. Success depends on a variety of factors, including estimated beneficial and adverse effects, feasibility, and event rates of the target population. As the phase II trials by definition do not have sufficient power to define the effect on major clinical outcomes, the estimate of treatment effect and harm may depend on multiple inputs, including effects on biomarkers, or on more common but less definitive clinical outcomes (like unstable angina rather than myocardial infarction).

**One of the traditional phase II designs in cancer is based on the work of Gehan, which is a two stage design. In the first stage, the investigator will attempt to rule out drugs which have no or little biologic activity. For example, he may specify that a drug must have some minimal level of activity, say, in 20% of patients. If the estimated activity level is less than 20%, he will choose not to consider this drug further. If the estimated activity level goes beyond 20%, he will add more participants to get a better estimate of the response rate. A typical study for ruling out a 20% or lower response rate usually enters 14 participants.**

If no response is observed in the first 14 participants, the drug is considered not likely to have a 20% or higher activity level. The number of patients added depends on the degree of precision desired, but ranges from 10 to 20. Thus, a typical cancer phase II study might include fewer than 30 people to estimate the response rate. Bayesian designs for phase II studies require prior estimates, the same case as for phase I studies, but differed in that they are priors of efficacy measures for the dose or doses to be investigated rather than of toxicity rates. Priors are useful for incorporating historical data into the design and analysis of phase II trials.

## PHASE III/IV:

The phase III and phase IV trials (Late Phase Trials) are the clinical trials that are generally designed to assess the effectiveness of




new interventions or existing interventions with new indications and hence, their value in clinical practice. Phase III trials of chronic conditions or diseases often have a short follow-up period for evaluation, relative to the period of time the intervention might be used in practice. In addition, they focus on efficacy or effectiveness, but knowledge of safety is also necessary to properly evaluate the role of an intervention in clinical practice. A procedure or device may fail after a few years and have adverse sequelae for the patient. In 2014, the FDA warned that morcellation to treat uterine fibroids by laparoscopic means, a procedure that had been used for years, could lead to spreading of unsuspected uterine sarcoma. Hence, long-term surveillance of an intervention is believed to be effective in phase III trials and is often necessary.Such long-term studies or studies conducted after regulatory agency approval of the drug or device are referred to as phase IV trials. Drugs may be approved on the basis of intermediate outcomes or biomarkers, such as blood pressure or cholesterol lowering. They may also be approved after relatively short term studies (weeks or months), even though in practice, in the case of chronic conditions, they may be taken for years or even decades. The late phase clinical trials are limited in size to several hundred or thousand (at most, a few tens of thousands) of participants. Yet the approved drugs or devices will possibly be used by millions of people. This combination of incomplete information about clinical outcomes, relatively short duration, and limited size means that sometimes the balance between benefit and harm becomes clear only when larger phase IV studies are done, or when there is greater clinical experience. For e.g. some of the cyclooxygenase 2 (COX 2) inhibitors, which had been approved for arthritis pain, but only disclosed cardiovascular problems after larger trials were done

**Continuum of Increasing Evidence Sequential Phases of Developing Randomized Controlled Trials.**

As stated above, the ideal clinical trial will have both randomization and double blinding, which will discussed further in coming sections of this series on clinical trials research

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# THE PHASES OF CLINICAL TRIALS

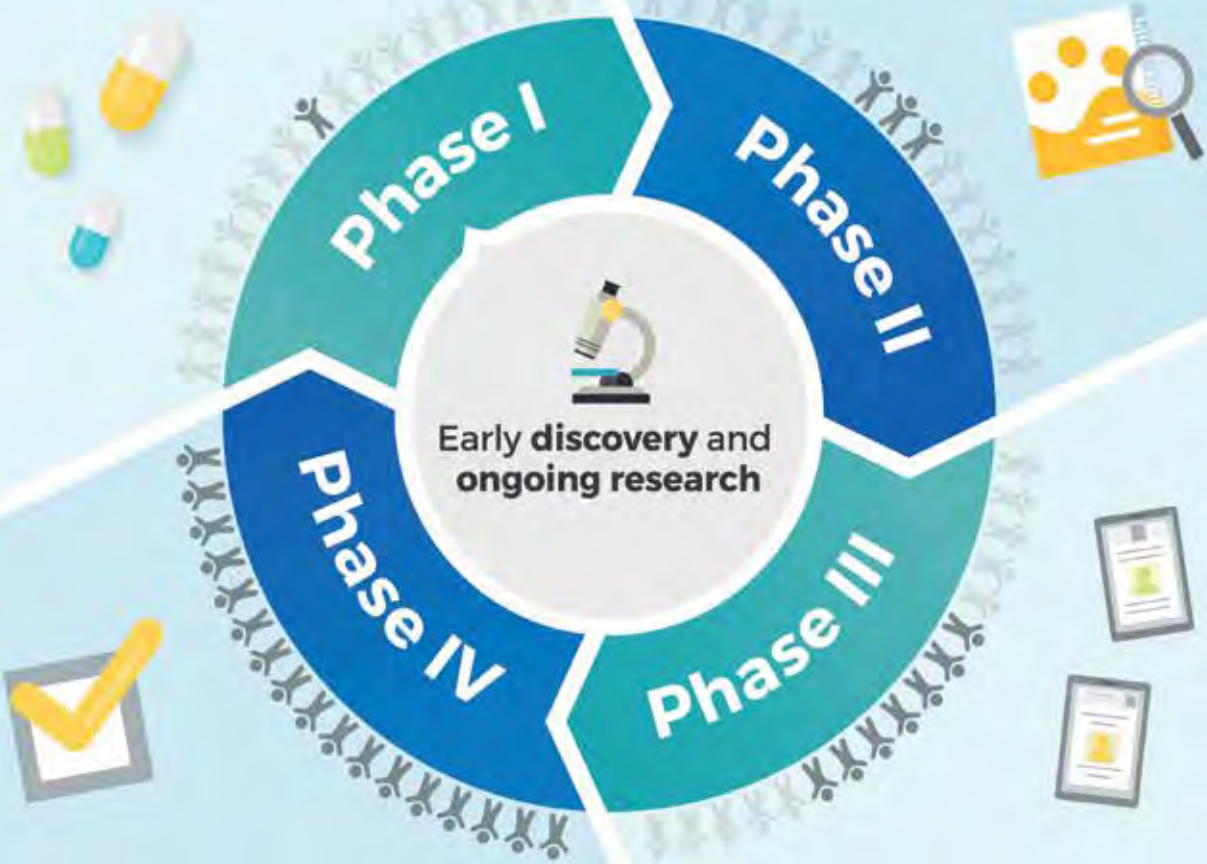
HUNTSMAN CANCER INSTITUTE
UNIVERSITY OF UTAH

**Safety** and best **dosage** levels are determined.

**1** to **2 dozen** participants

**Response** to new treatment is recorded and analyzed.

**Fewer** than **100** participants




Treatment is **approved** and marketed.

**Thousands** of people involved

**Results** are compared between **new** and **standard** treatment.

**Hundreds** of participants

| | PHASE 0 "Exploratory" | PHASE I | PHASE II | PHASE III | PHASE IV |
|---|---|---|---|---|---|
| Description | First-in-man early trial to determine if the drug engages its expected target | Initial safety evaluations, determine safe dosage range, identify common side effects, and study toxicity profile of the drug. | Begin to explore efficacy while maintaining safety. | Final confirmation of Safety and Efficacy. | Any trials conducted after FDA approval of the drug. |
| Number of Subjects | 10-15 healthy volunteers | 20-80 healthy volunteers | 100-300 volunteers with the targeted medical condition. | 1000-3000 subjects with the targeted medical condition. | Number of subjects depends on trial endpoints. |
| Dose | Single, low dose (<1% of dose calculated to produce a clinical effect) | Single dose Single ascending dose Multiple ascending dose | Multiple dose trials, often conducted against placebo. | Multiple dose trials, ascending doses. | Variable |
| Endpoints | Not expected to show clinical effect or significant adverse effects. Helps to choose between competing chemical analogs for further study. | Escalation of dose ends when unacceptable side effects occur; the previous dose is considered the maximum tolerated dose. | Explores clinical effects against the targeted condition, and reveals the less common side effects. | Confirms clinical efficacy of the drug against the targeted condition and evaluates safety and side effects. | Confirms clinical efficacy and safety and explores other possible drug uses; may be required as a condition of drug approval. |
| Timing | Can be conducted with prior approval while final IND review is pending. | Together with Phase 0 trials, first clinical trials conducted in an IND process. | Conducted after report to FDA of results of Phase I Trials. | Conducted after report to FDA of results of Phase II Trials. | Conducted after the release of the drug by the FDA for marketing. |

# Section 02

# STUDY DESIGNS:
## FACTORIAL DESIGN

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Randomized control trials are gold standard in terms of clinical decision-making. The three features of RCT which confer advantage over other uncontrolled experiments are randomization, blinding and a placebo-control group. Through randomization, investigators ensure that characteristics, which are known, like socio-demographic characteristics, and those that are unknown, like genetic predisposition, immune status, etc., are balanced between the two groups. Randomization only ensures balance when the sample size is large enough. One way randomization can ensure a balanced base line characteristics is by stratifying the groups according to variables which are known to have prognostic significance (like age, gender, comorbidity status, etc.).

This notion seems surprising that one of the most robust aspect of research design is left to chance alone i.e. randomization. The randomized clinical trials are serious endeavors in the matter of cost and the risks involved in generating the best practice evidence around the globe. The clinical trial research has accelerated in recent years with added complexities of the interventions in themselves. In order to design the studies well, the right science of clinical trials is to be considered in its essence. The study design in general is constructed way before the actual recruitment of participants. The conventional parallel arm trial has well defined principles for design and analysis. Contrary to the popular belief the analysis of the clinical trial is simple contingent on the design of the trial. If the design is constructed right, the analysis is easy and straight forward. However, there is an increasing awareness that some of the assumptions do not turn out to be as they are made at the beginning of trial. The adaptive design challenges some of these assumptions and takes in to account the information as it gathers. The conventional parallel arm study designs are usually well understood; the designs complementing or alternating the conventional one are becoming increasingly popular and warrants discussion.

Factorial trial design is of choice when there is a need to test the efficacy or safety of multiple treatments simultaneously. The basic design of factorial method is built to test the effectiveness of (at least) two active interventions against a control. The independent variables are tested for their effect on dependent variable individually and together. These two or more independent variables (or active interventions) are known as '**factors**'. Each factor has subdivisions called '**levels**' (see table 2);

a study having two factors that each has 2 levels is called a 2 x 2 factorial design. Similarly, in a trial with three factors with 2 levels each, the design will be 2 x 2 x 2 ; the interventions will be assessed in the combination of 2 x 2 x 2 (8) groups with each unit randomized at least 3 times into various combinations of treatment plans.

In a factorial design, the simplest arrangement is 2 x 2 that means in a balanced 2 x 2 factorial trial for two interventions X and Y , N/2 subjects will be randomly assigned to treatment X and N/2 will be randomly allocated not to receive treatment X. Similarly, N/2 subjects will be assigned randomly to receive treatment Y or not to receive treatment Y (see table 1).

**Table 1. Groups in 2 x 2 Factorial Design**

| | N/4 | N/4 | N/4 | N/4 |
|---|---|---|---|---|
| **Treatment X** | X | - | X | - |
| **Treatment Y** | - | Y | Y | - |
| **Subjects randomized** | *Treatment X* | *Treatment Y* | *Treatment X + Y* | *Control* |

The statistical analysis of factorial trial reveals its power (See table 2) in the analysis phase. Analysis is carried out usually by comparing subjects who are randomly assigned intervention X (i.e. those who received treatment X and those who received X + Y ) with those who are not assigned to intervention X ( i.e. those who received treatment Y and those who received not treatment at all ) Likewise, subjects randomized to intervention Y (i.e. those randomized to Y and those randomized to X + Y ) are compared with those not assigned to intervention Y (i.e. those assigned to X and no treatment at all) .

**Factorial design assumes that there is no interaction between the combinations of interventions tested in the study.** They are, therefore, not statistically powered to detect any such interactions. However, this assumptions needs validation during the study analysis .The possible interaction can be tested by inclusion of interaction term between the interventions in a regression model and then comparing the same model after excluding the interaction term. The sample size calculation for factorial trials also assumes the absence of interaction between the treatments. Consider a simple 2 x 2 factorial design as a two arm parallel design for ease of calculating sample size. The target effect size are then calculated for each treatment separately in similar fashion. The comparison that offers larger sample size is considered for the enrollment of participants since this will be powerful enough to detect the effect of the other treatment group. This method is similar to parallel arm trial and is followed for factorial trial for a reason; it ensures that the power of comparison is based on the subjects in a group being compared and not on the overall number of subjects in the study.

**Example:**

A multicenter double blind randomized controlled trial of 2 x 2 factorial design was conducted to assess the efficacy of minocycline or celecoxib as an adjunctive treatment in bipolar depression. Each patient was allocated once to each treatment, hence every patient was randomized to one of the four arms resulting in four treatment groups:

Patients who received minocycline only. Patients who received celecoxib only. Patients who received both minocycline and celecoxib. Patients who received neither (placebo).

The use of factorial trial made it possible to perform two comparisons concurrently at the expense of one experiment. In this trial it is possible to compare improvement in bipolar depression in patients who received adjunctive minocycline with those who did not receive minocycline by comparing the columns. Likewise, by comparing the rows it is possible to compare the efficacy of celecoxib (see Table 2). Table 2. Treatment groups after randomization in a 2 x 2 factorial design randomized controlled trial testing the efficacy of celecoxib or minocycline as adjunctive treatment for bipolar depression (Husain MI, Chaudhry IB, Hamirani MM, et al Neuropsychiatr Dis Treat. 2016;13:1-8. Published 2016 Dec 19. doi:10.2147/NDT.S115002)

| Table 1. Groups in 2 x 2 Factorial Design | | | | |
|---|---|---|---|---|
| | N/4 | N/4 | N/4 | N/4 |
| Treatment X | X | - | X | - |
| Treatment Y | - | Y | Y | - |
| Subjects randomized | *Treatment X* | *Treatment Y* | *Treatment X + Y* | *Control* |

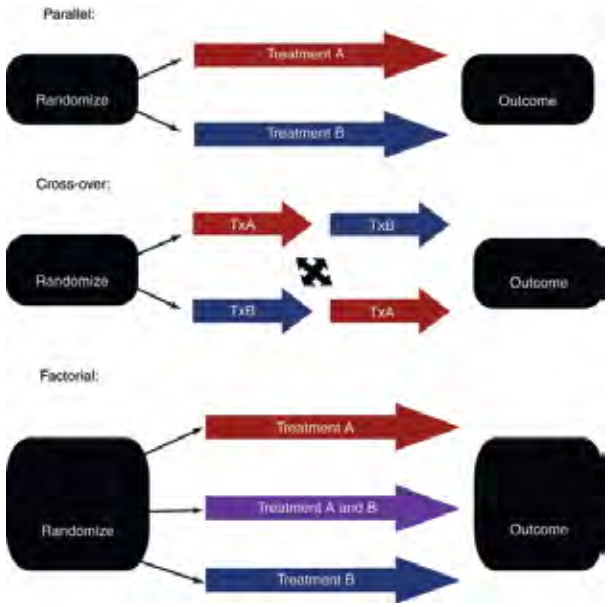
**Table 2. Example of 2 x 2 Factorial Design RCT**

| Celecoxib | Minocycline: Yes | Minocycline: No | Overall |
|---|---|---|---|
| Yes | Celecoxib + Minocycline (n = 68 ) | Celecoxib only (n = 66 ) | Celecoxib (n = 134 ) |
| No | Minocycline only (n = 66 ) | Placebo (n = 66 ) | Non-celecoxib (n = 132 ) |
| Overall | Minocycline (n = 134 ) | Non-minocycline (n = 132 ) | Total Patients ( n = 266 ) |

The different types of factorial studies have rather unique mathematical representations. The types can be based upon number of factors as well as their levels and are represented by variable product terms: for example a 2 x 3 design means a treatment with 2 levels and another treatment with 3 levels resulting in six groups. It can be used for sequential treatment strategies. The other classification is based on how many treatment combinations are assessed in the study. If every combination of interventions is tested, it is called '**fully crossed factorial design**'. If some intervention combinations are left out from evaluation it is called '**incomplete or partial factorial study**'. Reasons for conducting later type of studies can be feasibility, necessity, cost or ethical considerations.

**The great advantage of factorial design is its cost effectiveness**. Factorial Design is economically beneficial over multiple arm parallel studies or several trials testing the interventions separately. If the power of study is kept same, a 2 x 2 factorial trial requires lesser number of subjects in contrast to a three arm trial for comparing multiple treatments. In an additional cost to one trial of a single intervention, multiple interventions can be tested and compared for their efficacy by using factorial design.

Along with its obvious advantages, the factorial study design has its own limitations. One of the **limitations** of factorial design has to do with the practical management of the trial. With the increasing number of interventions, handling and management of the trial becomes challenging. The other disadvantage is related to the compliance of the participants. Participants may be unwilling to try multiple combinations and go weary of the participation over time. Specifically, the participants randomized to one or two interventions will be more compliant than those who are randomized to multiple interventions. The adherence will be reduced unevenly and this imbalance can powerfully impact the overall results. Judicious use of placebo or combination pills (multiple treatments within a single pill) can curtail this problem. However this might be difficult in practice because of the expenses, as well potential biochemical interactions, between agents. As mentioned afore, since most factorial trials are designed with the assumption that there is an absence of interaction between interventions, they are underpowered to detect any effect that rise with a probable interaction in the subgroups.



# CLINICAL TRIAL DESIGN:
## CROSSOVER TRIALS

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Crossover trials are study designs in which each subject receives more than one intervention (usually both active and control treatments) in either order for an identified duration. There is a 'washout' period between interventions. This cross over ensures that each subject acts as his own control. The switch between treatments is usually separated by washout or restabilization phase. This is an important component which ensures that the effects of first treatment can fade away. The sequence of treatments is generally randomized and blinded.

The crossover trials are divided into two classes on the basis of numbers of interventions assigned to subjects; if the subject receives all treatments it is a 'complete crossover' and if each subject receive some of the treatments it is called an 'incomplete crossover trial'. The most basic cross over design is a two treatment, two period trial, in which each subjects receives treatment A or treatment B in first period of trial and then the other remaining treatment in subsequent period. This crossover design is written as 2 x 2 AB/BA trial. The sequence of treatment is randomized and usually half subjects receives treatment A first and other half treatment B and vice versa in the succeeding period(Fig 1).

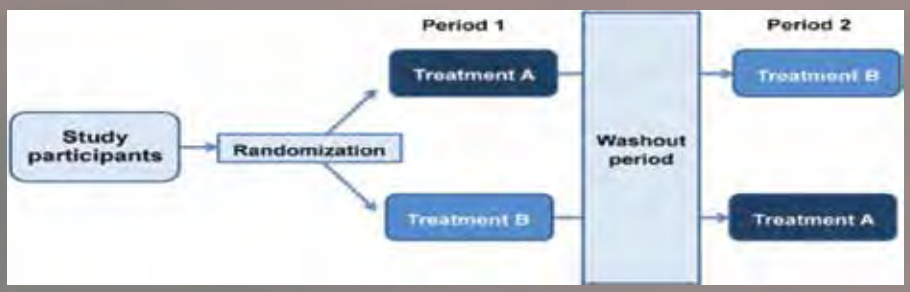



Figure 1. A Simple 2 X 2 or AB/BA Crossover Design

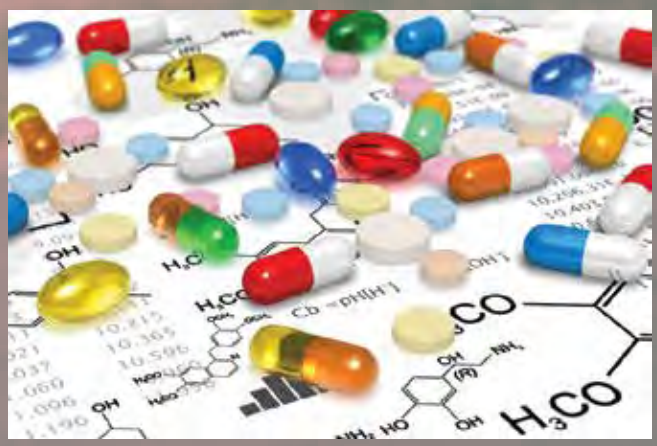
It is important to note that in crossover trial the treatment difference is based on comparisons within subject than between subjects. Since each subject is his or her own control, the variability (within a subject) is less hence the precision of findings is increased. Fewer participants are needed to find the treatment difference than those required in a parallel arm study. The resultant smaller sample size is an obvious advantage and can be expressed as:

$$N_{CROSSOVER} = (1 - r)\, N_{PARALLEL} / 2$$

Where, r is correlation coefficient among repeated measurements of primary endpoint, and it indicates that as the correlation approaches 1 sample size can be reduced ranging from half of that needed in parallel arm study (if r is 0 ) to quarter of that required for parallel arm trial (if r is 50%) ..

The reservations to crossover trial design is the inconvenience to the participants that arises from receiving multiple treatment with various transition periods. The noncompliance and withdrawals from treatment can seriously hamper the trial and imbalance between arms and phases can result in incomplete data and faulty results.

The assumptions for crossover trials must be met at the beginning of trial. This



requires the subjects to be at similar stage of illness at the start of trial; the conditions suitable to crossover trials are therefore chronic and stable in nature such as rheumatoid arthritis or chronic schizophrenia.

Crossover trials have their optimal utility in early drug development phases such as Phase I pharmacokinetic studies; bioequivalence trials; studies for proportions and maximum dosages; and Phase II pharmacodynamics trials.

The other obstacle in crossover trials is to identify and manage the 'carryover' effect. Carryover effect is the effect or physical presence of first treatment that remains persistence (carried over to) in the next treatment phase. The examples can be of a drug given as treatment A that is detectable in blood sample when sample is drawn after giving treatment B; or it can be psychological such as memory of improvement during first treatment affects the perception or judgment about subsequent treatment.

The carryover effect has the potential to pollute results in a way that researcher will be unknowingly gathering combined effect of treatment rather than separate effects. Besides some statistical methods to cater to this problem, the best possible way is to provide adequate washout period between treatments or a close monitoring between the phases. Second significant problem can be due to 'period effect'. It is the difference in effect of a treatment caused by the sequence i.e. whether it is given first or second in sequence. This effect persists even after adequate washout period such as in hypertensive drug trials. The solutions can vary from equalizing allocation to both sequences to some advance statistical methods.

# TRIAL DESIGN:
## CLUSTER RANDOMIZED TRIALS

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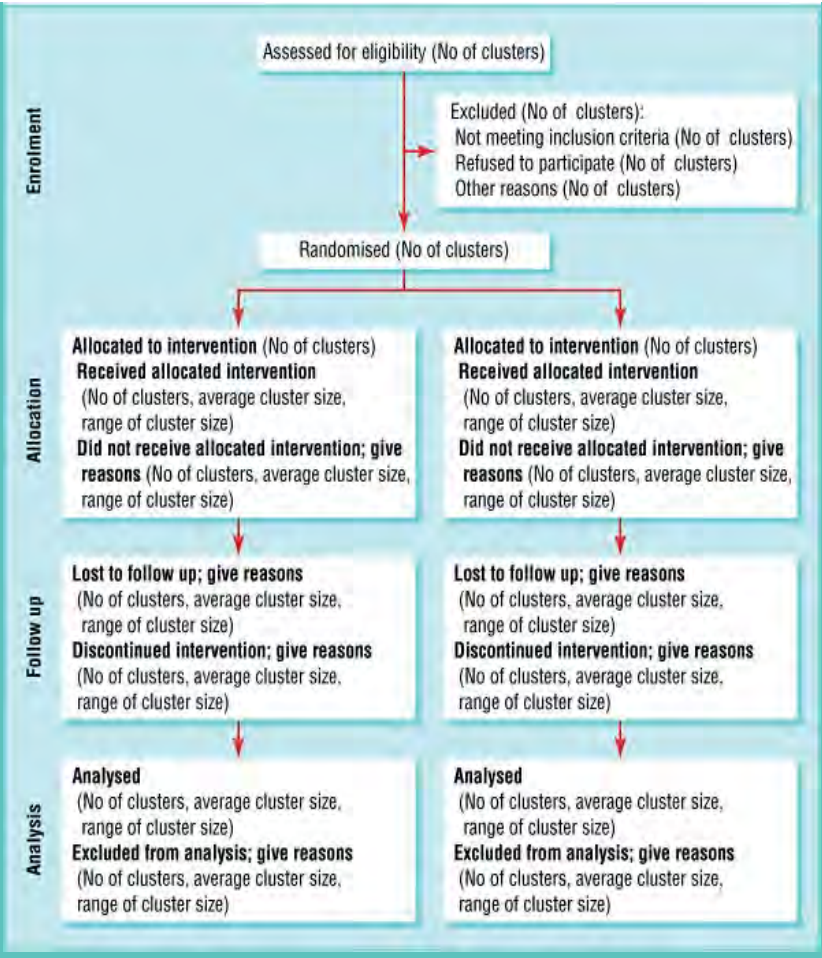
A cluster randomized trial is a study design which randomizes groups of participants rather than individuals. Cluster randomized trials (CRT), also known as **Group randomized** trials, are one of the best comparative designs when the desired intervention cannot be delivered at individual level. When there is need for **community level interventions**, like educational programs for childhood malnutrition, training of general practitioners to manage depression and addressing clean water supplies in villages, CRT design is preferred Initial step CRT involves defining and choosing the clusters. Geographical demarcation, towns and villages make natural clusters to intervene. However, they can be different in terms of variables like households, socioeconomic status etc. In such cases stratification is done within a cluster while using these variables. Randomization is done, then, at each stratum. This stratification also increases the power to detect effect estimate in each arm.

Figure 1. Example of diagram showing flow of clusters and participants through a trial adapted from doi: 10.1136/bmj.328.7441.702




The design and analysis of cluster randomized trial require special methods to make them appropriate statistically. Of note are the concepts of design effect and cluster correlation. The people within a cluster manifest resemblance to each other that violates the "independence" assumption underlying analytical methods for Randomized Controlled Trial. Shared experiences, interaction among participants and common exposures can be accountable

for such correlations in an organizational unit or groups thus leading to correlated results. This correlation is quantified by Intra class or Inter cluster correlation coefficient ICC. It is important to control ICC in CRTs since this lack can negatively affect statistical powers of trials. One should assume certain considerations with cluster randomized trial analysis. When sample size is inadequate, it increases the

Other issues that need vigilance in such design may include generalizability, imbalance between study arms and poor control for intra or inter cluster variability.

In calculating sample size of complex randomized sampling such as cluster randomization, '**Design effect**' is used to adjust variance for an estimator of a parameter; where the variance is caused by not using simple random sampling (SRS) .Design effect (Deff) is a real number and is a ratio of variance of two estimators, Deff <1 signifies that the given sample design has less variance than SRS design while Deff>1 signifies that the sample design has variance greater than SRS design. The sample size for cluster randomized trials using above parameters can be:

$$N_{CLUSTER} = (1 + [m - 1] \times ICC) \times N_{SIMPLE}$$

- Where, $N_{CLUSTER}$ and is sample size for cluster randomization and $N_{SIMPLE}$ is for simple randomization
- **m** is number of participants in each cluster
- **(1 + [m – 1] × ICC)** is design effect
- **ICC** is intercluster correlation coefficient

Example: A study was conducted to test the effectiveness of a manualized parenting integrated program known as Learning Through Play (LTP+) in maternal depression and child socio-emotional development belonging to a low resource setting (N Husain et.al 2021) . For the purpose, a cluster randomized trial was designed.

For the study of the 400 villages of Gadap Town (one of 18 towns in Karachi), 120 were selected on basis of catchment area, safety and local area leaders' cooperation. These 120 villages were taken as 'clusters' and each village was the unit of randomization. 60 randomized villages were allocated to intervention (LTP+) arm and 60 to TAU arm. Mother and child dyads, of child being 0-30 months were the participants in each cluster.

The sample size was calculated to be 294 mothers, 265 after 10% attrition rate at 6 month follow up and 90% power to detect using results from a previous cluster RCT from Pakistan with ICC 0.09 and effect size 0.2. The randomization at village level renders participants of same village to share similar outcomes, therefore, multilevel regression methods were used with villages and participants as random factors and others as fixed factors.

Cluster randomized trials provide a complementary study design to conventional trials. Cluster trials are design of choice for assessment of quality enhancement strategies in healthcare and education systems. There are certain **limitations** with cluster design. Larger sample size is required for CRT because there is a potential loss of power for the same number of participants in a CRT as compared to conventional RCT design. One of the other significant risk associated with cluster design is contamination.

**Contamination** happens when any aspect of an intervention is adopted by individuals from control arm due to contact with individuals from intervention arm, thus diluting the treatment contrast in a randomized controlled trial. For example if the clusters are connected geographically or through other close means, participants can talk and share knowledge with each other ;

this may directly affect the treatment results based on its nature or indirectly because of the unblinding done due to communication between two treatment arms.

# CLINICAL TRIAL: STEPPED WEDGE DESIGN

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Stepped Wedge Trial (SWT) is a relatively novel research trial design. It can be thought of as a variation of cluster randomized trial differing in a baseline period, allocation strategy and other features that set it apart from a conventional parallel arm design.

It is gaining popularity for evaluation of service delivery or policy implication type interventions in larger communities. SWTs are useful designs for Phase IV trials which require rolling out of intervention at population level. The pragmatic nature of SWT is advantageous but also warrants cooperation from individuals in clusters.

**Stepped Wedge Randomized Trials constitute of a design in which clusters (or individuals) receive the interventions over a number of points in time until almost all the clusters have received the intervention;** the order in which the clusters receive the intervention is randomized and data is collected over time at every step ( point where every group receives the intervention). Data points in control section of wedge are compared to those in intervention section to test the effectiveness of intervention.

The term stepped wedge was coined during the Gambia Hepatitis Intervention Study initiated in 1986 by The Gambia Hepatitis Study Group. Previously, this stepwise approach had been used in trials labeled as 'phased interventions' or 'waiting list design'. But Gambia Trial was probably the largest and earliest formal example of a Stepped Wedge Trial design (SWT) study. It was a large scale Hepatitis B vaccination project in infants that was to be followed for 30 to 40 years. The objective was to determine efficacy of HBV vaccine in prevention of hepatocellular carcinoma and chronic liver disease. The design of the study gained popularity and was termed stepped wedge because of its stepwise wedge shape visible in the schematic illustration of the study design (see Fig 1). The prior evidence of HBV vaccine efficacy prompted its sequential rollout. The geographically defined areas were randomly allocated to incorporate HBV vaccine in their infant vaccination programs at 10-12 weekly intervals until infants of whole nation are covered in around four years period of time .

**a** = Duration of Trial

**b** = Total Number of Clusters

**c** = Cross Over Point

**d** = Step Length

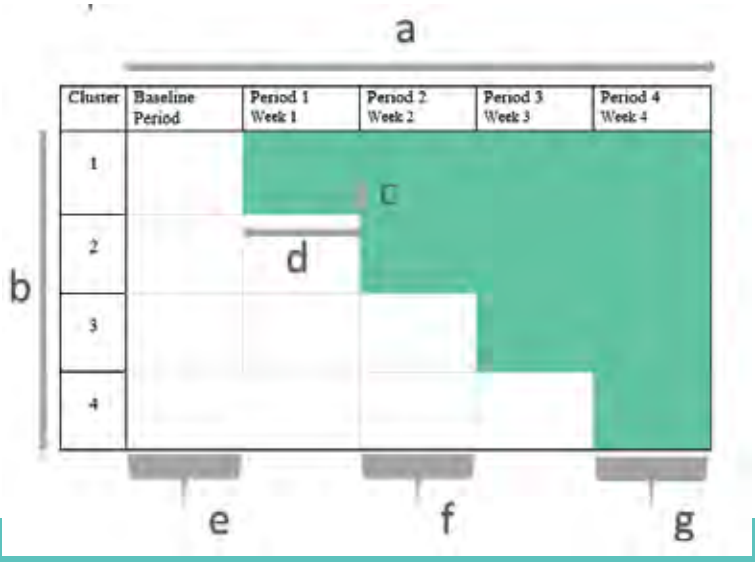
**e** = Pre-Rollout Period

**f** = Time b/w 2nd & 3rd Cross Over Point

**g** = Post Roll Out Period

**Unshaded Area** = Control

**Shaded Area** = Intervention




Cohort for liver disease is on follow-up since then. In the initial phase no cluster receives the intervention. Afterwards, one cluster or group of clusters is randomly assigned to intervention i.e. crossed from the control to intervention. This procedure is repeated at pre-defined intervals (steps) until all clusters receive the intervention. Data is collected throughout the study; it is of note that each cluster grants two sets of information one as control when it has not received the intervention, second after it has been crossed over and receives the intervention. This is in contrast to parallel cluster design in which clusters are randomized to two arms of control group and intervention group; in SWT the 'arms' are replaced by observation periods and exposed vs unexposed observation periods are compared with each other. Therefore, the summary of trial should include the characteristics of subjects and clusters as per their exposure status. The other key feature of SWT is that the crossover (transition from current to subsequent group) is usually always unidirectional i.e. from control group to intervention group.

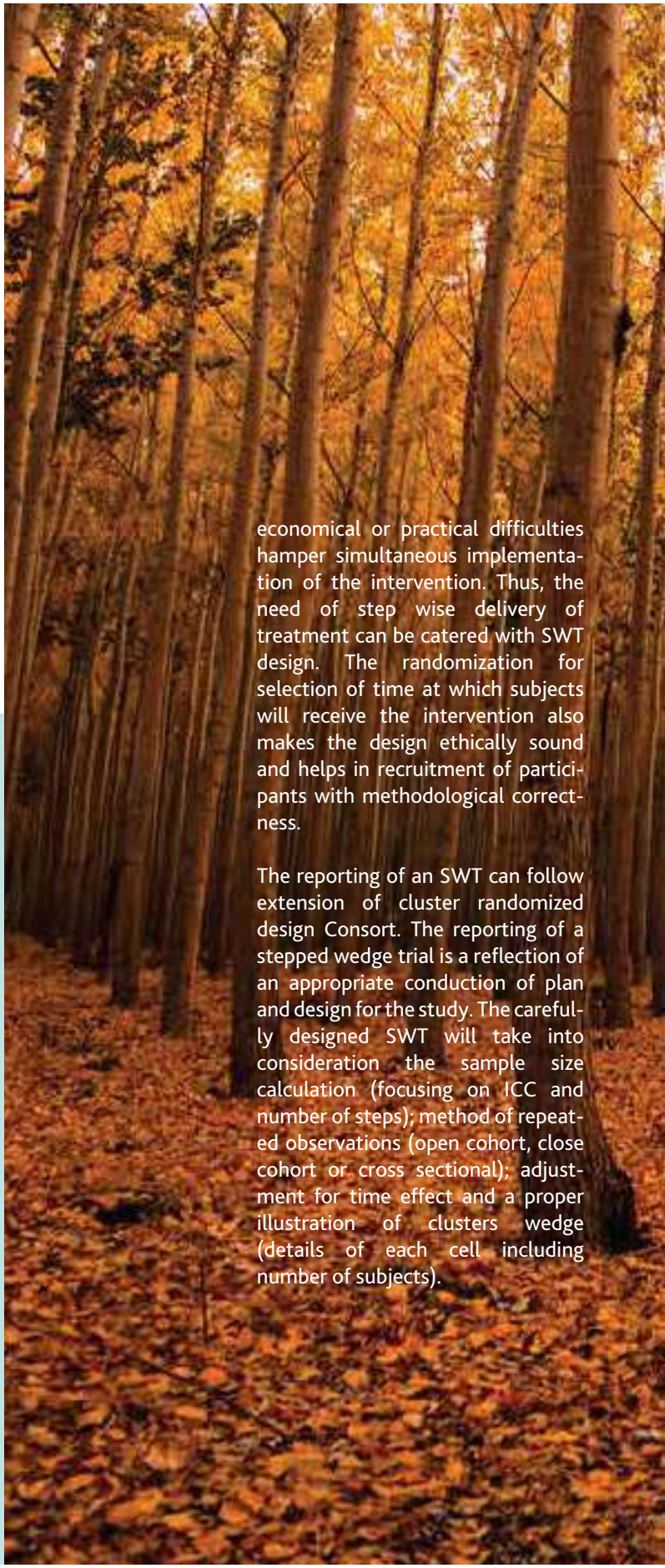
The **outcome data** can be collected in following ways: cross sectional data- when the data is derived from single measurement taken from individual subjects and at each step data is collected from different individuals. Longitudinal data- when the data is collected from repeated measurements of the similar group of individuals who have participated from start to follow-up. Open cohort – when data is collected through mixture of both above mentioned methods.

The allocation strategy for a stepped wedge randomized trial is defined by its features that distinguish this design from others. **'Rolling out'** is the delivery of intervention to randomized clusters. **Cluster** is a set of individuals and constitutes a unit of randomization. Common examples of cluster include small villages, communities, wards in a hospital or healthcare facilities. A **crossover point is a point** at which control group becomes the intervention group. There can be transition period while crossing over. This transition period is defined as special acknowledgement of time spent in incorporating the intervention into a cluster. At this point the clusters are not be considered as either exposed or unexposed. A step is considered to be a cross over point where as **step length** is the length of time between two successive steps and is constant throughout the trial. These intervals must be long enough to ensure full effect of intervention takes place. The totals steps along with their step lengths determine the total number of clusters as well as the total duration of the study.

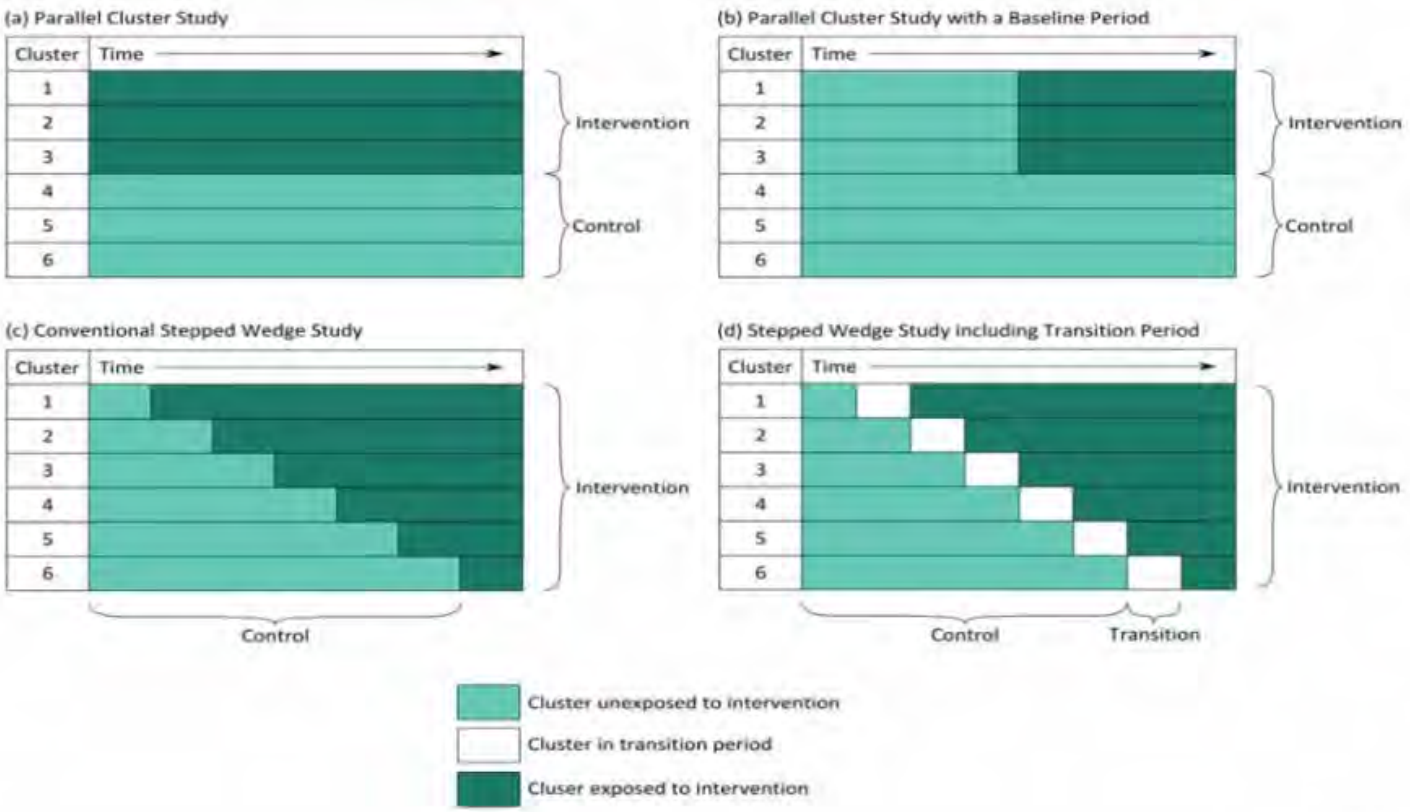
There are certain design considerations of a stepped wedge trial. While designing a SWT the number of clusters, number of steps and duration of each step are need to be decided in advance. These design choices are dependent upon many factors. Foremost is feasibility and logistics, for example, number of clusters can be limited by accessibility to desired clusters. The length of each step and how many clusters will be randomized to intervention at each step also can be determined by system's capacity to deliver the intervention. The other features of design that are not restrained by logistic reasons can be determined by keeping other aims in mind such as enhancing statistical power of the trial.

The **statistical aspect** of an SWT poses a number of challenges. The sample size calculation needs the allowance produced by the confounding effect of calendar time. This is different from parallel cluster studies where no time effect is present. The other difference resides in its special feature i.e. in SWT each cluster gives observation in both states as exposed and unexposed to intervention thereby each cluster acting as its own control. This can increase the precision of study given if intra cluster correlation ICC is large. Other features on which the power of an SWT depend include strength of treatment effect; number of clusters; number of steps; number of participants per cluster per step and equality among cluster sizes.

There are certain situations in which a Stepped wedge trial design seems desirable over conventional parallel arm design. Firstly SWT becomes relevant in situations where there is evidence for the intervention to be more beneficial than harmful rather than being equipoise. In these cases, it becomes ethically concerning to hold back the useful intervention from a fraction of the population. Also if a classic cross over design would have been employed, withdraw of the favorable intervention would be wrong. Secondly, there are circumstances where logistical, economical or practical difficulties hamper simultaneous implementation of the intervention. Thus, the need of step wise delivery of treatment can be catered with SWT design. The randomization for selection of time at which subjects will receive the intervention also makes the design ethically sound and helps in recruitment of participants with methodological correctness.



The reporting of an SWT can follow extension of cluster randomized design Consort. The reporting of a stepped wedge trial is a reflection of an appropriate conduction of plan and design for the study. The carefully designed SWT will take into consideration the sample size calculation (focusing on ICC and number of steps); method of repeated observations (open cohort, close cohort or cross sectional); adjustment for time effect and a proper illustration of clusters wedge (details of each cell including number of subjects).




## Example:

An effectiveness study of Covid-19 vaccine [Sinovac's Adsorbed COVID-19 (Inactivated) Vaccine (Projeto S)] was conducted in the town of Serrana Brazil (April 2021). In the study, deferred vaccination technique was opted.

Deferred vaccination is timely access of vaccine to placebo groups; it is used in situations where it is not suitable to maintain population on placebo yet gaining enough time to attain insight about effectiveness and other information regarding the vaccine. To ensure whole targeted population ultimately get the access to Covid-19 vaccine in a phased and sequential manner, a stepped wedge design was used to generate real world evidence while keeping in logistic and ethical considerations.

In this trial the Serrana towns were divided into four clusters (see Fig 1). Each cluster was randomly allocated to any of the four subsequent weeks. At the start of study every cluster was considered as control or unexposed observation group. In each week enrolled participants in one cluster received first vaccine dose and thus crossing over to become intervention or exposed observation group. This was repeated for four weeks until all four clusters (a total of 2,700 individuals) were vaccinated against the Sinovac's Covid-19 vaccine.

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# CLINICAL TRIAL DESIGN:
## SUPERIORITY & NON-INFERIORITY TRIAL DESIGN

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RCTs are designed according to the scientific research question. Superiority trials demonstrate that the latest treatment whether drug intervention or psychotherapy intervention is superior or better than the control group. A rule of thumb is to specify the null hypothesis opposite to what we expect for the outcome. For example, if treatment A is better than treatment B, the null hypothesis is that A is not better than or same as B. It is anticipated that the data will reveal, otherwise the null hypothesis is rejected in support of the anticipated superior treatment A.

According to Chow and Liu, assessment of superiority is usually done in two steps. The first step is to demonstrate that the treatment group is significantly different by testing the hypotheses. If the null hypothesis is rejected, and the sample mean value in the treatment group is larger than the control group, then it is claimed that the treatment group is superior to the control group. This two-step procedure is equivalent to testing the superiority.

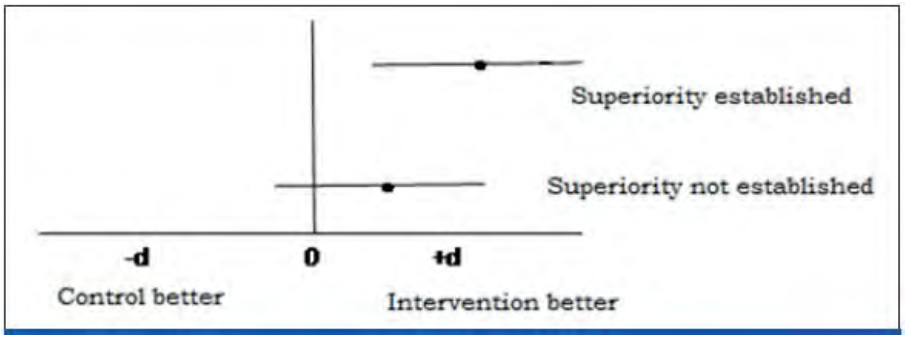


Figure 1.Superiority Trial Design

Recently medical science demonstrates an increasing interest in conducting non-inferiority trials, they have been introduced in 1990s with the impression that the latest treatment would be better than the standard treatment due to some important considerations. Non-inferiority trial designs are complicated and its assumptions are difficult to verify because patients are theoretically exposed to treatment inferior to gold standard. They are different to superiority trials, which intend to demonstrate that a new treatment intervention would performs better compared to a control group. Poor quality of trial can bias trial findings in concluding differences among treatment groups, generates more challenging impact on non-inferiority trials than superiority trials. Even if the latest treatment demonstrates to be inferior to the gold standard treatment, it still show subsidiary benefits such as less technical risks, low cost or less side effects.

A randomized controlled superiority trial accessible to relatives of individuals with psychosis or bipolar was conducted across the UK. The objective was to determine clinical and cost-effectiveness of The Relatives Education and Coping Toolkit (REACT) including a Resource Directory (RD), versus RD-only. A nested qualitative study examined participants experiences of (REACT), which is an online supported self-management toolkit designed to improve access to NICE recommended information and emotional support for relatives of individuals with psychosis or bipolar. 800 participants were recruited based on the predefined inclusion criteria, randomized into two groups. Primary outcome was relatives' distress (GHQ-28) at 24 weeks.

Distress decreased in both groups by 24 weeks, with no significant difference between the two groups. Findings indicate that REACT is an inexpensive, acceptable, and safe way to deliver NICE-recommended support for relatives. However, for highly distressed relatives it is no more effective in reducing distress than a comprehensive online resource directory (Fiona Lobban et al., 2020) Randomised controlled superiority trial)

Non-inferiority trials are established when a placebo controlled trial is not feasible ethically and the treatment is not expected to better than the existing acceptable intervention in terms of efficacy, but apparently better in terms of secondary outcomes, such as safety, costs, compliance or convenience. The non-inferiority trials seek to assess whether the latest intervention is not unacceptably inferior to the existing intervention. Although these trials are not used to establish better treatment efficacy.

Non-inferiority trial proposes subject matter related to the operational argument such as selection of the appropriate margin that might be considered subjective, but depends on the sign & symptoms of the clinical findings.

In many occasions, a well-defined estimate of the effect of control is required, which is not always accessible. Whereas in other situations, findings of equivalence trial establish due to

carcities in trial such as small sample size, lack of double blinding, lack of masked random allocation, improper doses of drugs, effects of parallel medicine or spontaneous recovery of patients without clinical intervention. It is critical that the pre-defined inclusion and exclusion criteria should be followed, similar to earlier superiority trials, to estimate the treatment group and the control group.

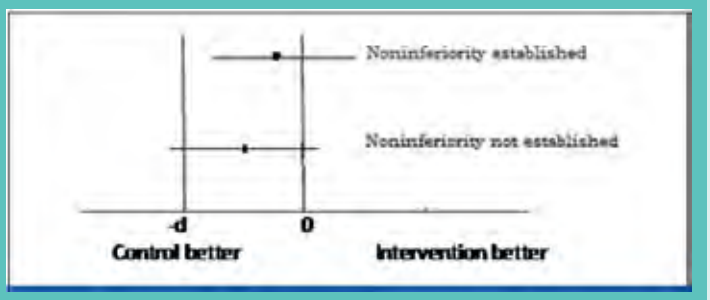


Figure 2.Non-Inferiority Trial Design

A cluster-randomized non-inferiority clinical trial was conducted to compare the effectiveness of home visiting paraprofessionals and mental health professionals delivering a postpartum depression preventive intervention. 874 women were enrolled based on the predefined inclusion criteria. Baseline assessments were conducted prenatally with follow-up extending to 24 weeks postpartum. Depressive symptoms at 24 weeks postpartum was the primary outcome. Neither intervention arm was superior to usual care in decreasing depressive symptoms across the sample. The non-inferiority was evidenced as the estimated mean difference in depressive symptoms between intervention arms did not surpass the pre-specified margin of non-inferiority of two points. Although there were no statistically significant differences found between intervention and control arms, non-inferiority analyses found paraprofessional home visitors generated similar reductions in depressive symptoms as mental health professionals. Additionally, Mothers and Babies appear to reduce depressive symptoms among women with mild depressive symptoms when delivered by mental health professionals (Tandon et al., 2021; A cluster-randomized non-inferiority clinical trial.)

Superiority, or non-inferiority trial are generally analysed by using intention to treat or per protocol analysis: In a per protocol analysis, one compares patients according to the treatment received and includes only those patients who satisfied the inclusion criteria and followed the protocol properly. In a superiority trial the purpose is to decide whether the two treatments are different, an intention to treat analysis is generally established. Superiority trial tend to develop differences between the treatments. To ensure the best possible quality of the analysis, it is significant to gather detailed follow-up data of all the randomized patients as per protocol, irrespective of whether they have subsequently failed inclusion criteria, withdrawn from trial prematurely, or violated the protocol in some other way. In intention to treat analysis, all the intended patients will be included in the analysis, whether they followed complete trial protocol or not. The purpose is to minimalize the probable impact of dropouts or non-compliants in elucidating the findings. In reporting non-inferiority trials, the recognised issue is that they are planned and analysed like a superiority trial and the scarcity of a statistical significance is taken as indication of equivalence. Therefore, there is a need for a better understanding of how non-inferiority trials should be planned, performed, analysed and reported.

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# CLINICAL TRIAL DESIGN:
## COMPLEX INTERVENTIONS

Complex interventions (CI) are those interventions that comprise of multiple interacting components which may act dependently or independently to each other. There is no clear demarcation between a simple and a complex intervention design. Medical Research Council defines Complex intervention on the basis of various factors (Box 1). Hawe et al, 2004 describe them as 'interventions with varying forms in different contexts while still being in compliance to particular theory driven processes'. Other definitions focus on nonlinear pathway, several synergistic components and feedback loops in the interventions.

Complex interventions (CI) impose a challenge for their conduction, analysis and interpretation to researchers, stakeholders and health policy makers. CI are increasingly being adopted in versatile domains of public health: health behavior change programs, health and social policy interventions and numerous psychological interventions. The key feature of Complex Interventions (CI) is their context which establish their utility and transferability in the real world. The real conditions differ from experimental ones in a number of ways for example training level of professionals; delivering an intervention; standardized procedural differences and varying environmental contexts etc. Therefore, conventional trials such as individual parallel arm randomized trials carried out in experimental conditions give limited practical implementation in real life. To deal with such limitations, there is an ongoing exploration of suitable evaluation models. There is a growing focus on modifications of randomized control trial; adaptation trials and alternative trials such as pragmatic trials, cluster randomized trials and stepped wedge cluster trials and realist evaluation.

**Box 1. What makes an intervention complex?**

- Number of interacting components within the experimental and control interventions
- Number and difficulty of behaviors by those delivering or receiving the intervention
- Number of groups or organizational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted
- Adapted from: Craig P, Dieppe P, Macintyre S, Michie S, Nazareth I, Petticrew M et al. Developing and evaluating complex interventions: the new Medical Research Council guidance BMJ 2008

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# EQUIPOISE STRATIFIED RANDOMIZED DESIGN: STAR*D TRIAL

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Major Depressive Disorder is a common mental health problem, globally affecting 4.4% of the population. It is a leading cause of disability worldwide and a major contributor to the overall burden of disease. Approximately, 322 million people worldwide have Major Depressive Disorder (MDD).1Most people with MDD, have a chronic or recurrent course of illness which is often accompanied by significant symptomatology and disability.2

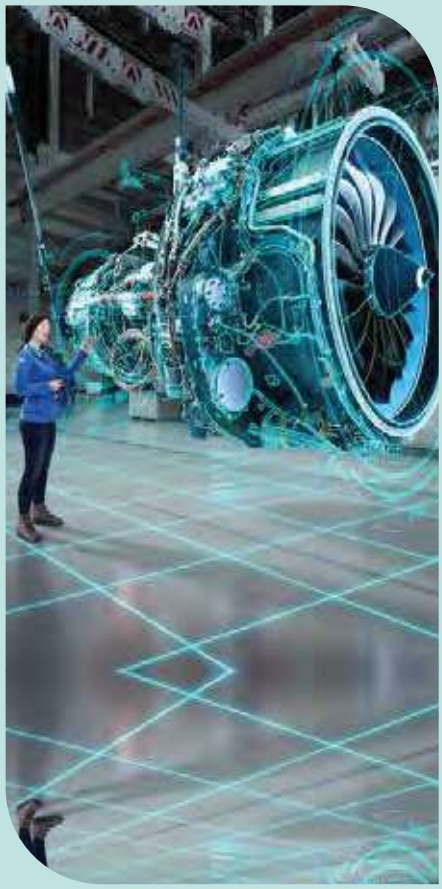
In the 1950s while work was being done on developing an anti-tuberculous drug, Iproniazid, it was observed that it has clear effects on improving mood and thus became the catalyst for developing antidepressants. It was classified as Monoamine Oxidase Inhibitor (MAOI). Simultaneously, Imipramine was developed as a byproduct of the search for new anti-psychotic. In the late 60s/early 70s SSRIs were first introduced as treatment for depression. Fluoxetine was the first SSRI developed and was approved by the FDA in 1987. Since then, citalopram, sertraline, paroxetine and escitalopram have also been approved by the FDA. 3

SSRIs have become the treatment of choice when treating depression. When we talk about treatment of depression, we use the terms response to treatment and remission. Response to treatment would indicate an improvement in the symptoms reported by the patient measured on a rating scale (HRSD) whereas remission would be complete absence of any symptoms or >50% reduction in symptomatology as measured on rating scale against a threshold.

Efficacy trials were done which reported remission rates of 22% to 40%. However these results could not be generalized to the clinical settings, as there was exclusion of patients with chronic depression, medical comorbidities and/or psychiatric comorbidities. The effectiveness trials done had low remission rates (11% to 30%) and high relapse rates during the maintenance period. Hence, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial was designed to find out which treatments are more effective following non-remission, intolerance to an SSRI or to any subsequent randomized treatment. It was a randomized study where patients were selected from both primary care settings and psychiatric clinics, who had not received benefit from initial anti-depressant.2

*The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) Trial is a landmark study published in 2006. It was funded by National Institutes of Mental Health (NIMH) and lead by A. John Rush, MD. It was the first and the largest prospective clinical trial of treatment of MDD which evaluated treatment strategies to improve outcome for real world patients with treatment resistant depression.4*
*The STAR*D Trial has over 120 journal articles published by the primary investigators, multiple citations by other researchers and media coverage which gives it a huge impact on the treatment of depression all over the world. It measured the effectiveness of 11 pharmacologically distinct drug-drug combinations.*

Star*D involved a consortium of 14 university based regional centers which included 23 Psychiatry and 18 Primary care clinics. The study duration was from 2000-2004. Inclusion criteria comprised of the following: patients aged 18-75



years, diagnosed as having non-psychotic MDD as per the DSM IV (Revised) and for which treatment with anti-depressants was mandatory. The patients were required to have a score of at least 14 on the 17-item Hamilton Scale for Depression (HAM-D17). Other primary disorders such as Bipolar Affective Disorder, Obsessive Compulsive Disorder, or an eating disorder were excluded.4

A total of 4041 patients were enrolled in the study, of which 234 dropped out after the baseline visit and 607 had a baseline HAM-D17 score of less than 14. The remaining 2876 participants entered level I of the study.2

STAR*D Trial employed an innovative study design feature called Equipoise

**STAR*D Algorithm: Treatment Levels**

| | | |
|---|---|---|
| **Level 1** | **Citalopram ( N= 2876)** | |
| **Level 2** | Patients could choose one of the following: (N=1439) | |
| | SWITCH (N=727) | AUGMENT (N=565) |
| | (Stop Citalopram, be randomized to receive one of the following)<br>• Bupropion SR<br>• Venlafaxine ER<br>• Sertraline<br>• Cognitive Therapy* | (keep Citalopram, be randomized to also receive one of the following)<br>• Bupropion –SR<br>• Buspirone<br>• Cognitive Therapy* |
| **Level 2a** | SWITCH (N=147) | |
| **(only for those receiving cognitive therapy in level 2)** | (stop cognitive therapy, be randomized to receive one of the following)<br>• Bupropion-SR<br>• Venlafaxine-ER | |
| **Level 3** | Patients could choose one of the following (N=377) | |
| | SWITCH (N=235) | AUGMENT (N=142) |
| | (stop current therapy, be randomized to receive one of the following)<br>• Mirtazapine<br>• Nortriptyline | (keep current therapy, be randomized to also receive one of the following)<br>• Lithium<br>• T3 thyroid hormone |
| **Level 4** | SWITCH (N=109) | |
| | (stop current therapy, and be randomized to | |
| | receive one of the following)<br>• Tranylcypromine (N=58)<br>• Mirtazapine plus Venlafaxine-ER (N=51) | |

** Patients could refuse cognitive therapy as a randomization option. All treatments were unbli nded. Patients advanced to successively higher treatment levels if they failed to achieve remission with their current regimen.*

Stratified Randomized Design. It allowed participants to accept or decline switch or augment treatment strategies as long as adequate options for randomization remained. Clinical equipoise refers to a genuine uncertainty in the expert medical community about whether a treatment will be of benefit. When considering entering a patient in any study, the clinician and patient must be able to define the list of specific study treatments that are acceptable. This list is called Equipoise Stratum. There must not be a treatment available that is known to be better than any of the treatments on the list.

STAR*D Trial was an Open-label Pragmatic study which means that it was an unblinded study. Both the investigators and participants knew which treatment they were getting. However the outcome assessment was blinded. Such studies although mimic real world clinics and they have the advantage of being easier to execute. The investigators are more comfortable in regards to their decisions about the interventions. The main disadvantage is of the possibility of bias. There would be bias in not only the participant's reporting of symptoms reduction and side effect profile but also the compensatory treatment or concomitant treatment they will receive. When joining the trial a lot of the participants have hopes of getting good treatment or the cure to their disease. If they get a drug that is known to them, or not new, or beneficial, they can easily become dissatisfied and drop out of the trial. Biased data collection and assessment can also be a hindrance with an open label study.

In this study, participants agree to randomization to all available options, exclude randomization to all available treatment options, and exclude randomization to all switches or to all augments at Level 2 (or 3), exclude or include cognitive therapy as a switch or augment, or exclude all medicines switches and augments at level 2 in favor of cognitive therapy.

The equipoise stratified randomization design yielded the following findings for the 1439 participants who had entered Level 2:

- 1% accepted randomization to all 7 treatment options.
- 50% accepted medication augment.
- 57% accepted medication switch
- 7% accepted randomization to medication switch and augment.
- 26% accepted randomization that included cognitive therapy.

- 3% accepted only cognitive therapy (switch or augment)

Most participants elected to allow randomization to switch or augment treatments (not both), hence the study was not able to compare outcomes for switch versus augment treatments. According to their protocol, it was recommended that the patients have their treatment visits at each level at baseline and then at weeks 2, 4, 6, 9, and 12 with an additional (if needed) visit at week 14. Participants who gained remission or received a sufficient response could enter a 1-year naturalistic follow-up period, however those who did not remit were advised to enter the next level of treatment. Those participants who had experienced intolerable side effects or reached the maximum dose with significant symptoms remaining were encouraged to move to the next level.

In the follow-up phase, the recommended visits were for every 2 months and the clinicians were advised to continue acute treatment at the same dose that was found to be effective. The outcomes were recorded using the interactive voice response system.

The primary research outcome was remission which was defined by a score of 7 or less on the HAM-D17 obtained by blinded telephone based assessors. Response was defined as 50% or greater reduction in the baseline QIDS-SR16 score. The HAM-D17 remission rates were generally less than those reported on the QIDS-SR16 due to the reason that the participants without an exit HAM-D17 score were deemed to be non-remitters. During this study, the treatment was delivered using the Measurement-Based Care (MBC). It would ensure adequate dosing for an appropriate period of time. MBC allowed for guided but flexible dosing recommendations at critical decision points based on symptoms and adverse effects 'measurements at each visit using the Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16) and the Frequency, Intensity and Burden of Side Effects Rating.

Of the 2876 participants, approximately 28% remitted based on the HAM-D17 and 33% remitted approximately based on the Quick Inventory of Depressive Symptomatology- Self Report (QID-SR16). The response rate which also included those who had remitted was 47%. Mean time to QID-SR16 remission for those who remitted within the 14 week period was 6.7 weeks. Mean time among those who responded was 5.7 weeks. A large number of participants at each level of treatment did not reach remission by week 6 or 8. Some remitted in week 14 or later. Approximately two-thirds of the participants did not remit with initial citalopram treatment based on the QIDS-SR16. Additional treatment resulted in decreasing remission probabilities. The cumulative remission rate after 2 steps was approximately 57%, cumulative remission rate for step 3 was 63% and step 4 was 67%.

Remission is less likely for the participants with a longer time since first episode onset, a longer length of current depressive episode, medical or psychiatric co-morbidities.The modest remission rates that result from multiple treatments, especially the third or fourth medication trials, also including the premature discontinuation of treatment by many participants highlight the need for more effective treatments.

There were no statistical clinical differences in the remission rates, response rates, or times to remission or response among any of the medicines compared in the study. All the medications used were safe and well-tolerated.

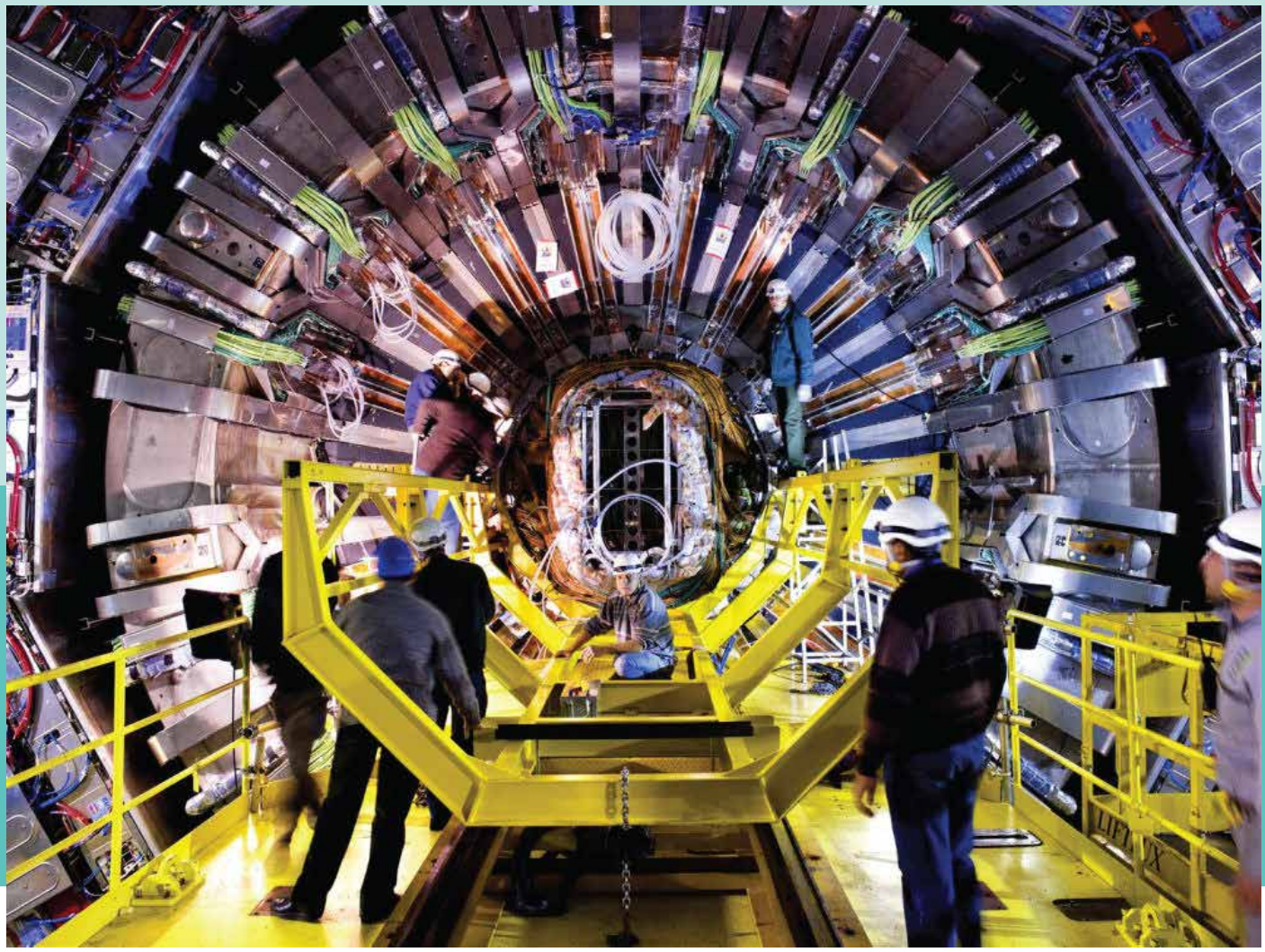
There was a high rate of relapse for participants in remission in the follow-up period. Patients who required more treatment steps had a shorter time to relapse and those who had responded but not remitted were at an even higher risk of relapse.

Relapse rates were calculated from those participants who had made at least 1 post-baseline call to the interactive voice response system. The relapse rates in remitted participants from step 1, 2, 3 and 4 were as follows: 33.5%, 47.4%, 42.9%, and 50%. There were certain criticisms made towards the study mainly stating the following points:

- Reporting of the response and remission rated using the non-blinded QIDS-SR16 instead of HAM-D17.
- Exclusion of patients who were started on citalopram at baseline visit but then dropped out before the exit HAM-D17 score in their primary analyses.

STAR*D's investigators found no significant differences between any of the 11 drug combination treatments and no secondary analyses had been done to show predictors of outcomes between the pharmacologically distinct treatments. STAR*D therefore, provides no next-step guidance for improvement of outcomes of treatment-resistant depression.

STAR*D's sequential treatment leading to remission using MBC care may have been detrimental to the patient, leading to poor outcomes as compared to clinical practice. It encouraged all participants who had not achieved remission to enter the next level of treatment based on a score, despite the fact that QIDS/HAM-D17 were not able to differentially weigh the core (low mood, guilt, suicidality or anhedonia) as well as the accessory (appetite, sleep, agitation) depressive symptoms and the patient's assessment of the relative importance of these symptoms.5 It may also have overestimated the importance of remission as compared to "just substantial improvement" as both these groups had high rates of relapse during the follow-up period. Also by encouraging the primary physicians to change anti-depressant when the patient had responded significantly to a drug so as to reach remission (HAM-D17 score of < 8), they failed to acknowledge the risk of increasing drug intolerance and study drop-out.5 Patients with poor sociodemographic status, psychiatric co-morbidities and minorities were more likely to drop out. It would be more advantageous to have direct outreach efforts towards patients who are at high risk of dropping out. Eliciting and addressing the barriers to treatment may be helpful as well as educational intervention regarding depression, it's course, expectations regarding improvement in treatment and the consequences of non-adherence and dropping out.



Efforts could be made regarding development of a treatment plan which would include not only an anti-depressant but therapy as well. Most of the patients in the STAR*D Trial had opted out of the switch/augment option to Cognitive Therapy. Those who had opted for it usually belonged to a better sociodemographic status and had more education. The high relapse rates in patients who had achieved remission also showed that we should not just work on the biological aspect of treating depression, but also the psychosocial aspect.

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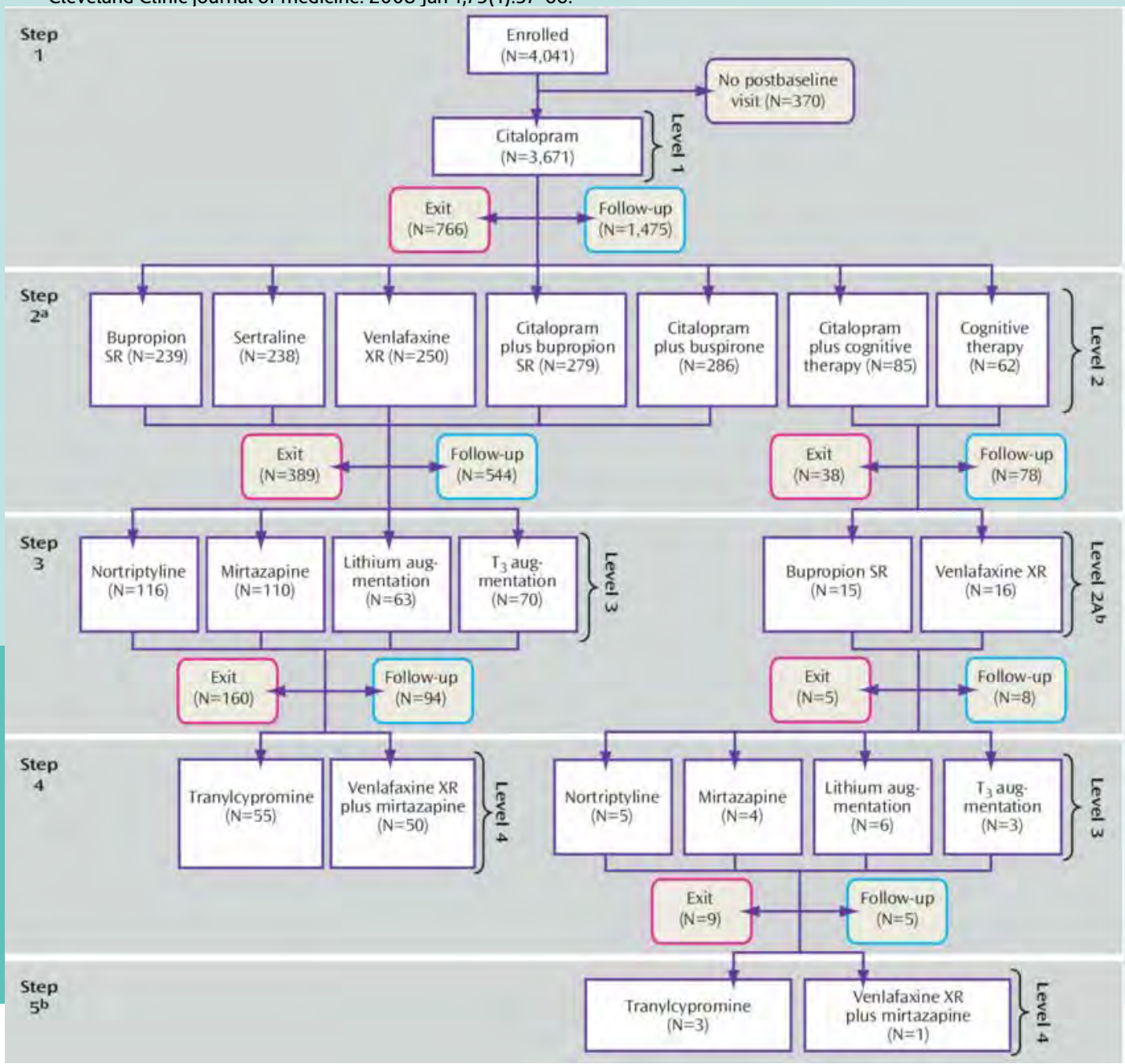

# ATYPICAL ANTIPSYCHOTICS
## AND WEIGHT GAIN

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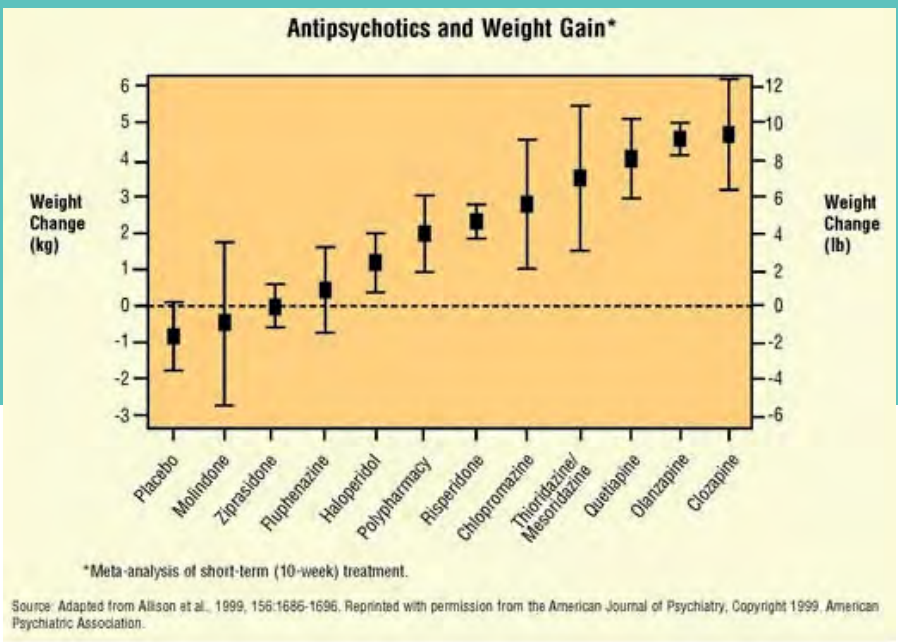
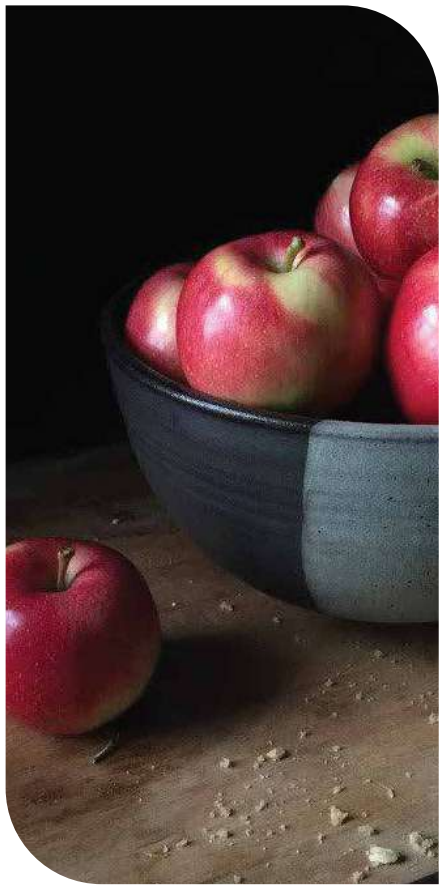
Obesity is one of the leading causes of global death and is one of the etiological factors in many morbid diseases. When compared to the general population the patient with mental illnesses have increased risk of cardiovascular disease and obesity , therefore escalating rate of mortality in the mentioned groups.Morever, Antipsychotics further add to the mortality rate by either direct cardiotoxic effect or obesity. Patients suffering from schizophrenia live 15–25 years less compared with the general population. [1] From psychiatry point of view schizophrenia and its treatment by antipsychotics are considered the main reasons for worldwide burden caused by weight gain.

Schizophrenia is a chronic lifelong illness of young people affecting all social classes with lifetime prevalence of 1% in general population. It severely impairs the personal and professional life and deteriorates the functionality of an individual and hisfamily. The discovery of antipsychotics represents the breakthrough in the treatment of schizophrenia. First with the development of typical antipsychotics, the symptoms of schizophrenia started to get better but with the price of their side effects mainly extra pyramidal symptoms (EPS) and tardive dyskinesia (TD), then atypical antipsychotics surfaced and marketed as antipsychotics with fewer movement disorders such as EPS and TD thereby started to replace the typical antipsychotics. But these atypical antipsychotics are also associated with another set of side effects like metabolic syndrome (diabetes mellitus, blood pressure changes, lipid profile disturbance, and weight gain), among these changes the weight gain is considered as the main cause of non-compliance of treatment.

The gain in weight varies substantially from drug to drug but virtually all drugs cause some degree of weight gain. The two agents associated with the highest weight gain (clozapine and olanzapine) appeared to produce between 4 and 4.5 kg of weight gain after 10 weeks of treatment on their standard doses whereas aripiprazole, amisulpride and ziprasidone appeared almost weight neutral. [2]



Factors associated with rapid weight gain in the initial period as indicated by studies include younger age, lower baseline body mass index (BMI), more robust response to antipsychotic and increase in appetite. Rapid weight gain of more than 5% in the first month is the best predictor for significant long-term weight gain. [1]

There is rapid weight gain in the first few weeks after commencing antipsychotics. The rate of weight gain then gradually decreases and flattens over several months. Time taken to plateau was different for each antipsychotic, ranging from 4 to 9 months for olanzapine and from 42 to 46 months for clozapine. This indicates that patients would continue to gain weight for 1–4 years. It is consistently reported that patients

continue to gain weight over time. [1]

The analysis of the complex relations over time between neuroleptics and weight gain in people with first episode schizophrenia in EUFEST study shows that the highest weight gain is in the first 3 months for all neuroleptics studied in EUFEST – Romanian cohort. [2]

But most of the time there is an adjuvant treatment that causes further weight gain like SSRI, TCAs, antiepileptics.The reason behind this effect on weight by neuroleptics is an interplay between increased appetite and decrease energy expenditure. A number of receptors are involved in causing weight gain such as serotonin antagonism, histamine antagonism, dopamine antagonism, and increase leptin levels. [4]

A recent meta-analysis of 78 studies explored trends in change of weight with antipsychotic treatment .The results showed with a period of 10 weeks treatment there is a change of weight 4.5kg on clozapine, 4.2kg with olanzapine, 2.1kg with risperidone, 0.9kg with ziprasidone [5]

The weight gain of more than 2.3 kg should be a clinical marker for the starting of a treatment plan which includes the 1) non pharmacological treatment and 2) pharmacological treatment. Non pharmacological treatment includes the periodic monitoring of weight and the recommendation for change in diet, physical activity and cognitive and behavioral strategies and all appear to be equally effective in individual and group therapy formats. A review on cognitive behavioral therapy showed significant results in preventing and reversing APP induced weight gain with corresponding weight loss of 4.87kg and 1.68 kg respectively.

If by above method the weight gain cannot be controlled, or patient is unwilling to do so then change of the drug to other with lesser side effect of weight gain is another option. Multiple compounds have been investigated as add-on medications to cause weight loss. Metformin has the best evidence in this respect. Burden of side effects needs to be considered when prescribing weight loss medications. There is no strong evidence to recommend routine prescription of add-on medication for weight reduction. [3]

Despite treatment advances in prevention, cardiovascular disease (CVD) remains the leading cause of mortality globally. CVD is responsible for 30% of all deaths and represents one of the leading long-term health considerations in the population as a whole.

Recent meta-analyses clearly indicated that long-term treatment with neuroleptics is associated with improved quality of life, decreased hospitalization, decreased aggressive behavior, and relapse prevention. [6]. Judicious use of atypical antipsychotics is essential for overall improving life quality of those suffering from mental illness.

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# Section 03

# MONITORING IN RANDOMISED CONTROLLED TRIALS: MITIGATION OF RISKS

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Randomised controlled trials are risky endeavours geared towards testing novel interventions which has a promise to provide effective treatment in circumstances when there is a room for improvement. They are controlled experiments intended to obtain answers which entail various risks. The three features of RCTs which confer the advantage over other (uncontrolled) experiments are randomization, placebo-control group and blinding. The important aspect of blinding (or masking) is that the participants, investigators and assessors are masked to treatment allocation and other important aspect of the trial conduct. This is intended to minimize the bias associated with the preconceived ideas1. It is important to provide an oversight on the outcome (measure) since experimentation involves risks. The risk can be associated with the intervention or (fatality of) the illness. The risk is further enhanced when the intervention involve use of placebo (and mortality as an outcome). The new intervention is also not without its own perils. Since the product is new the side-effects are mostly unknown. The investigational product developed through various stages of animal and human subject research also stands in trial - with careers and money at stake. This write-up will describe the newer developments in the clinical trial research related to the use of Data Monitoring Committee (DMC) and Interim Analysis of Results in clinical trials.

In the initial instance, there should be an ethically and scientifically valid reason for recruiting seriously ill patient in to the randomised trial and subjugating them to rigorous monitoring procedures. There has to be a clinical equipoise, among the community of experts, in order to carry out a controlled experimentation. This is not only a scientific but also an ethical prerequisite for conducting an RCT – uncertainty should lead to inquisitiveness and subsequent inquiry in the domain of science. However, (human) rights of individuals involved in the trial should not take precedence over intellectual pursuits and good of society through discovery, alleviation of suffering and greater good of many individuals. In certain conditions, patients are also desperate to seek new treatment, given the fact that illnesses are chronic and effective treatment is not available. With this background, patients are enrolled in the trial with the intent to keep a balance between therapeutic benefits entailed in participation in the trial and risks associated with trying out a new intervention. Monitoring the results by the physicians involved in the trial conduct is expected to disturb their initial equipoise of preferring one treatment over another. Given this state of affairs, the participating physicians might not be inclined to recruit patients to placebo (or treatment) group. As in general matters of life, someone has to be in charge of the situation. This responsibility is generally relegated to a committee of scientific experts who has the responsibility to examine the ethical, statistical and operational matters of the research according to a predefined schedule2.

Members of data monitoring committee (DMC) has to be, not only informed regarding the matters of science, but also matters outside the (accumulating data) trial. In fulfilling this task, they have to be independent, with no overt or covert conflict of interest. As ideal as it may sound, the financial, academic or intellectual and emotional conflict of interest has to be minimal and non-interfering with the conduct of trial3. Charged with this responsibility, the DMC should provide an oversight to the trial by reviewing the interim data. They intervene by advising the trial executive committee whether to continue or stop the trial early. The three conditions in which trial can be stopped early are called efficacy, safety and futility

rule. In the efficacy rule the trial is discontinued if there is a clearly demonstrated efficacy of one intervention over another with future recruitment unable to change the results. The safety rule pertains to clearly demonstrated harm to the trial participants which was unanticipated before the start of the trial. The futility rule of stopping the trial has to do with no favorable benefit of one intervention over another thereby reducing the harm of exposing the participants to inferior intervention or withholding otherwise effective treatment. The DMC can also advise (protocol) changes to the design, analysis or conduct of the study since they have an access to the accumulating data and interim results on efficacy or harm of the intervention4.

DMC has to have mix of representation from subject specialists, trialists, bioethicists and other professionals, who are independent (have no conflict of interest) and have access to unblinded trial data, on the primary endpoint and safety outcomes, as it accrues. There are statistical methods, based on group sequential (interim) analysis, of trial data as it accrues5. However, the decision to stop the trial is not based on statistical tests alone. There are corollaries which need to be considered. Phase III clinical trials are expected to provide evidence on the efficacy of drug/device beyond reasonable doubt, leading to change in clinical practice. Therefore sufficient evidence needs to be accumulated to establish the efficacy and long term safety of the drug/device. A premature termination may raise concerns related to long term safety of the compound6. There is no agreed definition of 'efficacy beyond reasonable doubt' in the context of regulatory approvals and litigations by current or future patients. However, statistics provides guidance in term of objective decision making. A collective wisdom of Data Monitoring Committee (DMC) is required to tackle the challenge facing the early termination of trial based on crossing of group sequential boundaries in the interim analysis for efficacy or harm, review of external evidence from other on-going trials or meta-analysis of existing data related to the trial7.

There are four general approaches to statistical monitoring of the interim trial results, allowing for early termination 8. The group sequential boundary approach does interim analysis on 'predefined time' of the trial as the data on primary (and secondary) endpoint accrues. The approach looks to plot the effect size on a graph with standardized Z-scores on the Y-axis and fraction of trial information on the X-axis. The sequential probability ratio allows for the continuous examination of the trial results. A triangular plot boundary examines the interim results, contingent on the null and alternative hypothesis, to lie in a range of values. Group sequential boundaries represent the accumulated wisdom of monitoring interim results in clinical trials given the nature of ethical/safety concerns related to participants in clinic trial. The conditional power (stochastic) approach takes in to consideration the (original) power calculation and its ability to answer the trial question given the results from interim analysis.

The paradoxical problem with interim analysis is that the data trends are subject to the random variation and fluctuation of results. The baseline characteristics of the recruited subjects and the (observed) effect estimates are also expected to be variable given the initial assumptions. Possibility of high risk subjects entering the trial early and leading to biased estimate of (higher) efficacy cannot be ruled out. Repeated testing can and does lead to false positive error rates9. The possibility of falsely

rejecting the null hypothesis is classically kept at 0.05%. When multiple tests are done this possibility is increased, if we don't take in to account the statistical assumptions related to repeated testing, thereby falsely rejecting the null hypothesis. The group sequential boundaries are constructed in order to reduce this risk especially early in the trial when data fluctuations are substantial. The false positive error rate is adjusted to be conservative early on with future increment to the industry standard (0.05) conventional to trials. This enables meaningful analysis keeping in view the statistical considerations of frequentists approach to statistics. Practical considerations is that group sequential approach guard against inadvertent false positive rejection of null hypothesis, based on random variation in data. The boundary philosophy also protects the alpha spending function at various stages of the interim analysis of data. Plotting of results on a graph with specified boundaries (also) informs the DMC on number of (positive) events required to have meaningful efficacy/harm results in remaining part of the trial. This not only checks on the underlying sample size assumptions but also enables the researchers to calculate the power required to check the difference in the two groups. If the initially hypothesized power (1-β) is unable to detect the meaningful difference, beyond the constructed (triangular) boundaries, then the trial can be stopped for futility. This consideration is equally applicable in the domain of harm/efficacy. The group sequential approach enables the DMC to re-calculate the power, given the underlying assumption on the event rate, during the conduct of the trial

There are three statistical tests based on alpha-spending function in group sequential boundry approach. These are Peto, Pocock and O'Brien-Fleming tests (Figure 1). Among the three the O'Brien-Fleming is by far the most robust approach. The O'Brien-Fleming boundary, divided over for four analyses, would estimate the false positive error rate to be 0.0001, 0.004, and 0.019 for 3 interim analyses while the final false positive error rate will be 0.043 which is nearly equal to the 0.05 standard significance level10. They can serve as pre-defined statistical stopping guidelines.. If the results of interim analysis cross these predefined statistical stopping guidelines then DMC could deliberate on the possibility of stopping the trial early. It also needs to look at the secondary outcomes which could warrant continued accrual of participants to offset any initial findings. If the aggregated data on two arms of the intervention has

no major concern on the primary and secondary outcomes then case can be made for early termination based on the efficacy. Decision to stop the trial early should only be made if there is reasonable evidence, beyond doubt, on the efficacy of the intervention. Additionally, evidence external to the trial should also be kept in mind during the DMC meeting examining the interim data.

There can be positive as well as negative consequences to more frequent interim analysis during the trial duration. The frequent monitoring of results has implications on cost, complexity of trial coordination and inadvertent unmasking related to (more) frequent monitoring. Contrarily it can be argued that multiple analysis would divide the data in to smaller bits (compared to four) thereby increasing the random variation in subgroup of participants and haste of conclusion. Frequent monitoring, however, is expected to inform the trial executives on the quality of study conduct and other operational measure which could be corrected thereby enhancing the trial integrity. The Chair of DMC needs to be well versed in matters of science as well as management. He/she needs to be a person who has background experience of conducting and supervising a clinical trial. Additionally, he/she should have no major conflict of interest. The chair of DMC is expected to take various actions based on the conduct of the trial as well as the contextual factors of the trial. Ideally he/she should base his actions on the rules set out in the DMC charter11. All major phase III trial should have written down charter, which should be signed by the principle investigator, the trial sponsor (Pharmaceutical company in case of a drug trial) and hospital administration or university leadership in case of a academic setting. The course of action would have been set-out or agreed upon during the initial meeting with the trial stakeholders.

The Federal Drug Authority in USA requires that Phase III trials which require licensing approval should have an external, independent DMC. If the risks are low as the drug has known toxicity or efficacy then case can be made for an internal DMC. The DMC can be internal or external to the trial executive committee or investigators. The reason for having an external/Independent DMC in phase III trial is that interventions are looking to test new investigational product in a serious medical condition with probably high morbidity and mortality.

The safety concerns dictate that there should be an independent monitoring. Additionally, the use of placebo and blinding makes the participating clinicians unaware of the segregated data on serious adverse events. Sometimes the follow-up is spread over course of months, after the initial intervention, favoring monitoring by external DMC. Argument against the external DMC can be that at times there are no known toxicity or life threatening complication associated with the intervention. DMCs can add complexity (and cost) to the data monitoring process especially in multinational trial setting. In such cases an internal DMC is constituted. The Internal DMC could comprise of executives, researchers and trialists who are employed with the same organization but are working on other projects. Care has to be taken that these individuals should not have any direct conflict of interest related to the task at hand.

The clinical trials research is increasingly getting organized in recent times with oversight from various regulatory authorities. The donor organizations, academic institutions and regulatory bodies are setting up their own guidelines for monitoring risks in research. It is time that certifying bodies like College of Physicians and Surgeons Pakistan develop policies, procedures and operational capabilities to monitor trials conducted under its ambit.

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# RESEARCH GOVERNANCE

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Research Governance is a set of regulations, principles and standards of good practice to ensure high quality research. Specifically, research governance is a process that sets standards for **professional research conduct**; defines **research management** including mechanisms to deliver standards, assessment arrangements; continuous compliance and monitoring for **managing funding and resources** and **risk mitigation**. Research governance improves **research quality** by; adherence to ethical and scientific quality, promoting good practice, reducing adverse incidents and ensuring lessons are learned to improve decision making and staff performance.

The scope of this paper is primarily to focus on research involving human subjects. Robust governance processes are to; protect human participants in research, clarify accountabilities and responsibilities of individuals and organizations involved in research, corroborate public benefits in order to maintain public confidence, as well as strengthen scientific quality of research.To fully understand the process of research governance, it is important for researchers to be familiar with some common terms in research and its execution. For example, **sponsor** is an individual or organisation (e.g. a university, a company, an institute, a trust, or a pharmaceutical company) that takes an overall responsibility and is held to account for a research for the initiation, management, and/or financing of a trial from start to end.The sponsor is responsible to meet high standards of good practice in research, set out research governance framework and the process by which it is implemented; and to ensure that arrangements are established and are in place for management, monitoring, reporting & audits. Most commonly, the **Principal Investigator (PI)** is the person designated to take overall responsibility for the design, conduct and reporting of a study. For multi-centre clinical trials, it is common to have the PI located at the main research site and local Principal Investigators (PI) identified at participating research sites. The project initiation arrangements include scientific review, ethical review, insurance etc. Additionally, there are arrangements related to management of the project; maintaining a site file, ongoing monitoring, reporting adverse events etc, and the project's financing arrangements.

There are five broad domains of minimum standards of research governance. These are;

1 **Quality of research design** - to maintain quality of research design, research institutes must make arrangements to facilitate internal peer review of research conduct within the remit of their institute.

2 **Ethics** - code of Ethics in research must be adhered to respect the dignity and rights of participants and to uphold their safety and well-being by having robust procedures such as gaining valid informed consent, and protecting confidentiality and privacy of research participants and their data.

3 **Information** - the information on research findings should be presented in a format accessible and understandable to research participants and, where appropriate, the general public.

4 **Health & Safety** - the health and safety of participants, researchers and other staff must be a priority at all times.

5 **Finance** - Research Institute Manager, with approvals from the Research Support Services, Research Finance and from the Research Institute Director must set out the funding arrangements for the research.


Research Governance is for all managers, supervisors, administrators and other staff, no matter how senior or junior. Moreover, all research projects must be independently peer reviewed i.e. through Research Ethics Committees

(RECs) before initiating a research trial. RECs safeguard the rights, safety, dignity and well-being of people participating in research. RECs review applications in order to give a view about the proposed participant involvement and whether the research is ethical. A favourable peer review must be granted for a research proposal to start.

**Ethics and Governance Working Group: An example from the Pakistan:** Institute of Living and Learning Pakistan Institute of Living and Learning (PILL) is a mental health research Institute with a track record of conducting large collaborative research projects with high profile institutions globally as well as working closely with the Parliamentary Sustainable Development Goals (SDG) Lead in Pakistan to develop mental health strategy for Pakistan. PILL is developing an Ethics learning hub and has set-up an Ethics and Governance Working Group (EGWG) in March 2021. The aim of EGWG is to set up an infrastructure of good clinical practice which is harmonious and responsive to the cultural norms and values of Pakistan, and serves as a vehicle of cascading learning internally within the organisation, as well as externally in Pakistan with an eventual goal of dissemination globally. As part of a review on Health Ethics in Pakistan, Rakhshi Memon (RM), the Chair, EGWG supported by Muqaddas Asif (MA), Lead Research Ethics and Governance at (PILL) found 1) bioethics in its infancy in Pakistan, 2) guidelines exist but implementation is patchy, 3) there is a lack of training of medical staff in clinical ethics, 4) there are deficiencies in institutional leadership and formal governance structures and 5) emergence of good practice - opportunity to formalise processes and to implement biomedical code of health ethics. Also, a recent research by Memon et al (2021) concluded that although the principles of autonomy, beneficence, non-maleficence and justice (Beauchamp & Childress 2013) serve as the prima facie four ethical concepts. It is however, crucial to scrutinise these Modus Operandi of the Global North in different cultural and social contexts. To bridge this gap, PILL has envisioned the ethics learning hub.

Based on the above mentioned findings and building on the good practice at PILL, the newly formed PILL's EGWG in collaboration with University College London, UK have embarked on the journey to develop ethics processes, resources and tools in their endeavour to plug the gap in culturally sensitive ethics processes, resources, tools and codes of practice. The group is working independently on different work streams including; 1) policy reviews, 2) conducting quality audits, 3) development of research ethics tool kit and work plan for trainings and curriculum with collaborators across the globe (Potential collaboration on bilateral learning with Great Ormond Street Hospital (GOSH), London, UK; Dublin City University (DCU), Ireland) on culturally sensitive toolkit development, and 4) publications and securing grants funding to resource the development of an Ethics Learning Hub at PILL. PILL is maintaining strict regulation of

governance procedures and International Council for Harmonisation Good Clinical Practices (ICH GCP). For example, almost 100 percent staff at PILL is trained in ICH - GCP. ICH was established as an International Association in 2015 with the aim to harmonise regulatory requirements around safety, quality and efficacy. (ICH, harmonisation for better health). ICH GCP is legally relevant only to clinical trials of investigational medicinal products. It was set up initially simply to help pharmaceutical industries agree with regulators how to avoid needing to repeat clinical trials of Investigational Medicinal Products (IMPs) in every legal jurisdiction. So, the emphasis is on harmonisation of regulatory rules. The initial work has grown in global prominence since the regulators in North America and Europe are still often regarded as the standard setters. This geo-political emphasis is changing and ICH will need to reflect that. There are other ICH guidelines which cover clinical trials of medical devices but none from ICH covering research generally, hence it highlights the need for a wider governance framework to lay out structures for proportionate oversight of different kinds of research activities and how they relate to non-research activities such as audit and service evaluation. Although, not mandatory, as part of the development of guidelines on safety, quality and efficacy ICH GCP has become an established model of international training in ethical and scientific quality standard for the design, conduct, recording and reporting of clinical trials involving human participation. This is to ensure the protection of the rights and well-being of research participants and that results of research are accurate and credible The ICH GCP curriculum is being reviewed in UK at present and as part of the consultation process, the EGWG have provided input to the working group on cultural sensitivity. **Acknowledgements:** We would like to acknowledge the dedication and hard work of EGWG members who are working towards developing the PILL Ethics Learning Hub. Rakhshi Memon, Muqaddas Asif, Ameer Bukhsh Khoso, Professor Mowadat Hussain Rana, Dr Salman Shahzad, Dr Noor ul Zaman, Dr Ayesha Ahmad, Dr Munazza Obaid, Jahanara Miah, Zaibunisa, Zaina Imam, Professor Sarah Edwards, Professor Nusrat Husain, Professor Nasim Chaudhry, Professor Imran Chaudhry, Dr Zainab Zadeh.

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# SYSTEMATIC REVIEWS:
## PRISMA GUIDELINES

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Well conducted systematic reviews and meta-analysis informs the readers on what works best in what conditions. Chalmer & Altman (1995) has defined systematic reviews as "reviews prepared using a documented systematic approach, in order to minimise bias and random errors"1. Systematic reviews are considered to be more robust then individual randomised controlled trials in terms of best practice evidence on the efficacy of an intervention2. A single trial is expected to be a point estimate among many other statistical inferences. Additionally, the random variation can be influenced by systematic error or bias associated with faulty conduct or analysis of trial3. Given the centrality of systematic reviews, various guidelines have come forth on how to report them correctly. An International group developed guidelines called QUOROM Statement (Quality Of Reporting Of Meta-analysis) in order to address the suboptimal reporting of results (1996)4. These guidelines have been revised, renamed as PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analysis)5. The PRISMA provides step-by-step guidance on the various stages of developing a systematic review. This allows the readers to assess the quality of the report. An omission, due to lack of reporting or conduct, at any stage of the systematic review can jeopardize the conclusions. The PRIMA checklist consists of seven sections, including the Title, Abstract, Introduction, Methods, Results, Discussion, and Funding. There are 27 items that provide readers with information regarding the eligibility criteria, searches, validity assessment, data extraction, risk of bias (within, individual, and across studies), synthesis of results, study characteristics, limitations of the review, and the funding for the review. In contrast to QUOROM, PRISMA requires that the objectives of the review include the PICOS reporting system (which describes the Participants, Interventions, Comparisons, Outcome(s), and the type of Study design). An important addition is the inclusion of Protocol and registration in the Methods section. This requires the authors to indicate if a review protocol exists, and, if available, provide registration information. It also requires authors to provide information on the sources of funding for the systematic review.

PRISMA guidance can help identify problems related to identification of eligible studies through database searches, screening of records and extraction of relevant material from the records, which can impact the pooled estimates by introducing various biases6. Publication bias can lead to erroneous conclusion of (statistically) significant outcome(s)7. Reporting of a comprehensive search strategy can identify potentially missing studies. Biased reporting of favorable outcome measures, avoiding adverse events, can also interfere with overall inference. PRISMA gives explicit guidelines on assessment of study level and outcome level bias. The reporting guidelines makes it explicit that various stages of the search and subsequent pooling is done in a way to make the reader aware of the potential pitfalls in the process of organizing and reporting of systematic review8. PRISMA guidelines recommends assessment of study quality which has to do with the conduct of the (actual) RCT. In the past, there have been many deficiencies in trial reporting and various suggestions have been made to improve reporting. These suggestions have included checklists and flowcharts and other forms of guidelines. The best known guidelines were produced by the CONSORT (Consolidated Standards of Reporting Trials) group (Schulz et al 2010)9. True to the adage, garbage-in, garbage-out, non-reporting of measures which are indicative of study quality will interfere with the review's conclusion. The study level factors have to do with the randomisation sequence generation, allocation concealment, blinding of the study participants/outcome assessors or events adjudication to treatment allocation; differential loss to follow-up, intention-to-treat analysis. The selective enrollment of (low-risk) patients could lead to selection bias, therefore threatening the validity of the results. Random allocation and concealment of this process ensures that recruitment of participants in to the trial is not influenced by preconceived ideas or preferences of the clinicians and participants, respectively. The internality of the trial is compromised due to differences in the baseline (socio-demographic) characteristics and the level of (prognostic) risk associated with the outcome. The external validity of the trial will also be compromised since the findings of the trial could only be extrapolated to the (near enough) characteris-

tics of those enrolled in to the trial. The proper reporting of these aspects, which represent the conduct of an RCT, allows the reader to assess the bias introduced in to the pooled estimate10. Previous research has shown that trials with non-rigorous methodology tend to overestimate the results thereby introducing an element of bias in the systematic review results. Therefore assessment of study quality allows the readers to make their own inference about the individual study and subsequent (heterogeneity) pooling of estimates. A formal assessment of heterogeneity, as specified in the PRIMA items, allows the readers to make their own assessment of the intra-study variation. PRISMA not only expects the reviewers to report the formal statistical tests of I2 but also guides the reviewers to report individual patient data (proportion, risk reduction) in each group11. The numerical data in the forest plot, with visual display of box and whisker image, allows graphical display to go along with facts. A separate forest plot for each outcome measure allows the readers to gauge the pooled estimate on important aspects of the study. Another important utility of PRISMA statement is the systematic description of missing information which allows the end users to identify potential areas requiring further research. A well conducted/reported systematic review informs the readers of potential gaps in the literature requiring further research. This has utility not only for practicing clinicians but funding bodies looking to allocate resources in order to make informed decisions. It is important that researchers in resource poor setting like Pakistan should use these guidelines. The cycle of knowledge can only be improved through doing (quality) research and reviewing (systematically) what has to be done. The identified gaps are especially relevant for designing studies which answer clinically meaningful questions in the context of Pakistan.

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# REPORTING CLINICAL TRIALS

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## Background:

Clinical trial reports are presented in a particular ordered structure known as 'IMRaD'. It stands for:

- Introduction
- Methods
- Results
- Discussion

Following section described the details which should be included in each section. This is relevant not only for reporting a trial but also reading a journal article on a clinical trial.

## Introduction:

The Introduction gives the scientific background on the reason why trial was conducted to begin with; clinical equipoise – a conflicting opinion between a community of experts – to justify an inquiry which will place a group of patients at risk for a definitive answer is the minimal justification for a clinical trial. One has to keep in mind that trial might not incur any obvious or tangible benefit for the participants. Generally speaking, if a benefit is accrued it will be useful for future patients, who will derive benefit from a new intervention free of risk or potential harm. Since patients are involved in the advancement of scientific question, as equal partners, they are called clients. The introduction summarizes what is known and what is unknown, both about the condition for which the trial intervention is intended. It also lay bare why a particular intervention is expected to be helpful. This may also include the objectives of the trial.

## Results:

The result section has received some attention in recent years with (even) guidelines to give a clear (diagrammatic) picture on the key findings. The result section should begin with a participant flow chart that describes the number of participants enrolled, allocated, followed-up, and analyzed in the trial. A table presenting the baseline demographic and clinical characteristics for each group will be included here. The main results are given for the primary outcome using the statistical methods, as described in the protocol. Any adverse effects, or secondary outcomes should also be essentially reported.

## Methods:

The method section described how was the trial carried out in sufficient details (trying not to leave things to imagination of the reader). This will include details of the intervention and how it was administered, the methods of selection for the participants and the method of allocation of the intervention. It is generally said that a reader should be able to replicate the trial from this information. In practice

restrictions on length of the manuscript will prevent a detailed description; however, on-line journals allow greater space or word count which is generally included as a supplemental material. The standard or operational definitions and methods (reference ranges in assays or laboratory investigation) for measuring the outcomes should also be given. The information about sample size is reported here therefore it is a good advice to curate a friendly relationship with statistician in all matters. The statistical methods for analysis and any computer software used for analyses should also be given n this section of the report.

## Discussion:

The discussion section has its own

purpose. The first paragraph generally repeats the main findings and subsequent paragraphs frames the findings in the context of other findings: what to the finding means? The object is to set the results in the context of current knowledge and to offer an interpretation for the findings. Possible explanations and hypotheses may appear, together with suggestions for further work, and any neurobiological basis is explained. This will also include description of the trial limitations, and the generalisability of the trial findings

## How Do We Report Trials?

In the past, there have been many deficiencies in trial reporting. Various suggestions have been made to improve reporting. These suggestions have included checklists and flowcharts and other forms of guidelines.

The best known guidelines were produced by the CONSORT (Consolidated Standards of Reporting Trials) group (Schulz et al, 2010). The CONSORT guidelines have been accepted by many journals to help authors improve reporting – they include a checklist of items which should be included when reporting a clinical trial and a flow diagram to show the passage of patients in a trial.

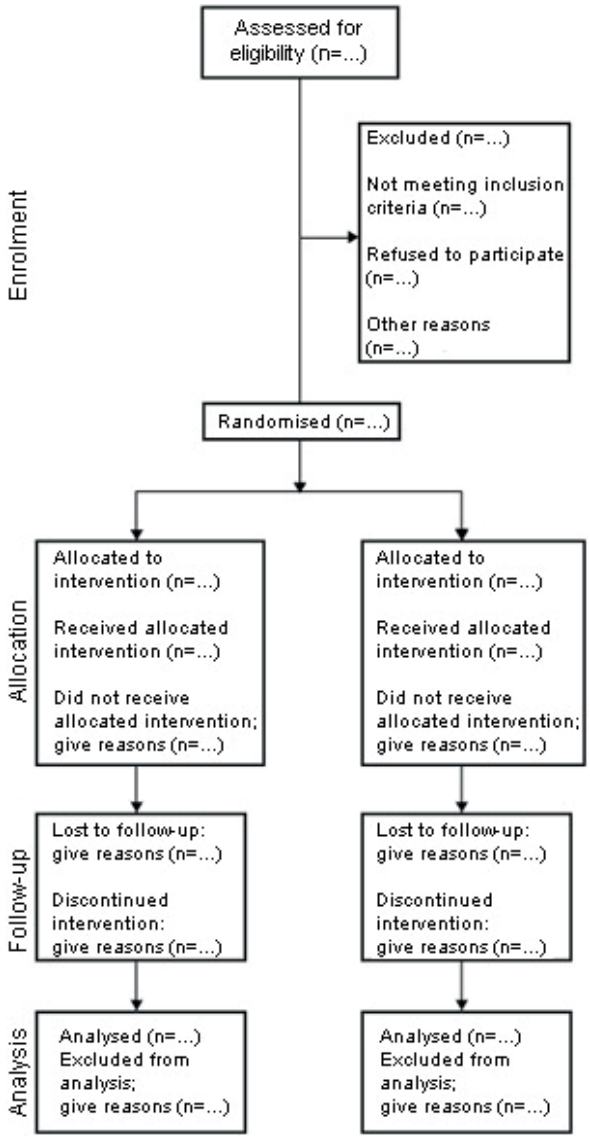
There is a CONSORT publication, together with explanations of the rationale for the elements of the guideline given by Moher et al, 2010. Additional papers covering topics not fully discussed in the main guideline, were published later; such as papers on reporting of harms by Ioannidis et al. 2004 and Abstracts Hopewell et al 2008a; 2008b; and on special trial designs, for example cluster randomised trials Campbell et al. 2004, non-inferiority trials Piaggio et al. 2006 and pragmatic trials Zwarenstein et al 2008. These are discussed in other section of Newsletter.

## Methods Section

The items listed in the Methods section (Moher et al. (2010) mentions subheadings that can be used to draw up an outline of the Methods section of the trial paper. It's important to note that writing an outline of the methods section helps clarify the order and content of the section, without worrying about how it is written.

The subheadings are used for our outline are as follows:

- Trial design
- Participants
- Interventions
- Outcomes
- Sample size
- Randomisation – sequence generation: Method of random sequence generation; type of randomisation
- Randomisation - allocation concealment mechanism
- Randomisation- implementation
- Blinding
- Statistical methods




The reader of a trial report needs to know details of the intervention(s) given to each arm of the trial. These details should include the formulation of drug, its dosage, timing, and duration of any treatment or vaccine given. Word needs to be put-in for the characteristics of any placebo given, including the manner in which it was disguised or the 'usual care' given to a control group, especially those receiving no alternative intervention. It is important to specify who administered the intervention, including their experience and any training in giving the intervention.

Trials often have more than one outcome. These can be subdivided into:

- Primary outcomes: these are the pre-specified outcomes that are considered most important to relevant stakeholders. Statistical analyses will focus on the primary outcome
- Secondary outcomes: these are other or additional outcomes of interest, which may include adverse events - unanticipated or unintended effects- associated with the intervention.

A report of each outcome measure should include the following when possible:

- The case definition for the outcome, including details of any diagnostic guidelines followed or validated measures used;
- Any methods used to maximize the quality of measurements (for example, training)
- The frequency and timing of outcome measurements;
- Specify who assessed the outcome;

If a trial reports no effect of an intervention, the reader of the report needs to be able to assess whether this is because there is no true effect in the population from which the study population was taken, or because the study sample size was too small to detect an effect. I

t is important to remember that the existence of sampling error means that whenever a hypothesis is tested there is a possibility of either rejecting the null hypothesis when it is true (type 1 or α error) or accepting it when it is false (type 2 or β error). The probability of a type 1 (α) error is known as the significance level of a test, while one minus the probability of a type 2 error (1- β) is known as the power of a test.

It is essential when planning a trial to calculate a sample size that will be sufficient to detect a clinically important effect with a specified level of significance and power.

The trial report or paper should provide information about how the sample size was

determined. Readers would like to know about the primary outcome that was used for power calculation, the quantities used, and the target sample size per study group.

This is where most clinicians struggle in writing their report. It's important that this is discussed this in advance with the statistician. Unlike the popular belief that statistician is needed only at the end of the trial when the data has been collected and needs tabulation for analysis. Statistician is most important part of the trial team and his/her expertise is needed at every stage – from design, conduct, analysis and reporting of trial.

Elements of the sample size calculation are: (i) the estimated outcomes in each group; (ii) the α (type I) error level; (iii) the statistical power (or the β (type II) error level); and (iv), for continuous outcomes, the standard deviation of the measurements.

The elements that we need to specify for a sample size calculation include:

- the desired level of significance ( )
- the desired power (1- )
- the baseline level of the primary outcome (for example, a baseline rate of 1/1000 person-years)
- the minimum size of effect we wish to detect (for example, a rate ratio of 2)
- (if continuous outcomes are used) the standard deviation of the outcome measurement in each group.

The sample size calculation needs to be included in the trial report, with enough detail to enable readers to reproduce the calculation if they wish. We should also state the results of the sample size calculation – in other words, the target sample size for each comparison group (including any increase in the sample size to allow for loss to follow-up during the study).

Reporting of sample size calculations are discussed on pages 7-8 of the Moher et al.

## 2010 CONSORT article.

Writing About Randomisation and blinding is most important part of the methods section. It is important to remember that valid comparison of treatments is enhanced by random assignment. Random allocation (if it is done correctly) is the only way we know that removes selection bias in the treatments given to participants in a trial. It results in groups that we know will, on average, be the same before the trial starts for both measured and unmeasured characteristics that might be associated with the outcome of interest.

There are three aspects to consider when reporting about randomisation in the Methods of a trial report. These are:

- How the random allocation sequence was generated
- Concealment of the allocation
- Implementation of the allocation sequence.

Unlike concealment, blinding of all parties in a trial may not always be possible. When writing a trial report, it is important to state which parties in the trial were blinded, the method used to ensure blinding (for example, use of dummy injections in a control group), how similar the treatments were (for example, the shape, colour and taste of tablets) and whether and how the success of blinding was evaluated (for example, by asking the blinded groups to state which intervention group they thought they were in).

## Results Section

When describing the results authors need to specify, how large was the effect of the intervention and how precise was this effect estimate? A valid trial is one which has addressed a clearly focused question, and where the methods used enable the results to be trusted. If the methods used are not of high scientific quality, then whatever the results reported, they cannot be relied upon. To consider the validity of a trial, it is helpful to address series of questions. These questions fall under three main headings:

1. Was the trial design valid?

- Was assignment of the intervention randomised, and (if so) was this done correctly?
- Was allocation of the intervention concealed from the patient and the recruiting investigator?
- Were the patients, investigators and evaluators of the trial all blinded to which intervention patients received?
- Were the intervention and comparison group similar at the start of the trial.

2. Was the conduct of the trial valid?

- How complete was follow-up of patients in each group?
- Apart from the intervention(s) itself, were the groups treated equally?

It is important to highlight how the results can be applied to the population of interest. We not only have to considered if the results of a trial are likely to be internally valid, taking into account the design, conduct and analysis of the trial, we need to consider whether these results are externally valid (generalisable to other populations), and how useful the intervention could be in these populations.

The question to answer is that to whom can we apply the results? This relates to those included in the trial and those who were excluded.

No trial is a random sample of the world population. Nevertheless, trial results can often be generalised beyond their immediate context which is the reason studies are carried out and results shared with the scientific world.

# CLINICAL TRIAL REPORTS:
## GUIDELINES FOR JOURNAL CLUB

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There is a huge explosion in the number of clinical trial reports, and subsequent teaching session including journal club presentations, it is feasible to report on how to read a clinical trial paper. This is also useful in planning or reporting of a trial. The fundamentals of clinical trials is repeated, strategically, to emphasize on the basics. It is not that those reporting clinical trials want to trick the reader into believing that methods followed were best, conduct flawless, and participants willing to die in the wake of good science but as it stands out researcher 'write-up' details to impress the reviewers and editors to have the paper published. Promotions, career and integrity is on the line besides the huge sum of money which sponsor might have invested in developing a drug or a programme in a complex intervention. In any case, a critical mindset is needed to decipher facts from fiction.

## The Trial Design:

**Was the trial design valid?**

- Was assignment of the intervention randomised, and if so was this done correctly?
- Was allocation of the intervention concealed from the patient and the recruiting investigator?
- Were the patients, investigators and evaluators of the trial all blinded to which intervention patients received?
- Were the intervention and comparison group similar at the start of the trial?

The first and foremost question which needs to be asked in about the design of the trial: *Are the Results Likely to be Valid?*

**Randomisation**

It is believed that comparison between treatments group is enhanced by random assignment of participants. Random allocation, when done correctly and reported accurately, is the best way to removes selection bias between the treatments given to participants in a trial. It results in groups, on average, to be the same before the trial starts for both measured and unmeasured characteristics. These prognostic factors might be associated with the outcome of interest. An important distinction to keep in mind is that It does not guarantee similarity in every instance. However, statistical analysis allows for chance imbalance that is associated with the outcome to be corrected especially when sample size is small. If an intervention is not randomised, the robustness of derived conclusions about the effects of intervention is made questionable and the results may be incorrect. Therefore, a failure to randomise properly must be justified clearly giving whatever the theoretical or practical limitations. If randomisation is done properly it should result in treatment groups to be similar with respect to all measured and unmeasured characteristics that might be associated with outcome of interest. This equal distribution of characteristics between groups is compromised when the investigator or the patient knows what treatment the patient is going to receive before the trial starts. This knowledge may have consequence on whether they are going to participate in the trial - a selection bias. With a promise of newer intervention having greater benefits lot of individuals who have serious illness or are non-responders will opt for the new drug. Drug or intervention might not be suited for a particular sub-group (non-responders in this example) and may be an effective therapy for drug-naïve patient due to pharmacokinetic reasons. The next thing to consider is whether the allocation of treatment was concealed from the investigator and patient before recruitment. This is a major endeavor since principle investigators are subjected to same pressures which are made to weigh heavily on civil servants or any public office bearers. Even wives (spouse) of P.I are used as an instrument for allocation to a particular group as reported by one investigator (who is not so happily married now!).

## Concealment

Was allocation of the intervention concealed from the patient and the recruiting investigator?

Sometimes the investigator or the patient can guess before the patient has been recruited onto the trial what treatment the patient is going to receive. This is a problem, because it may affect whether the patient is recruited. For example:

- If the investigator believes that the patient is less suited to the treatment that s/he has been allocated to compared to the alternative treatment, then the investigator may exclude the patient from the trial
- If the patient does not get the allocation that is their preferred option, they may decide not to take part in the trial and drop out.

The treatment group to which a participant is allocated is predictable then this may compromise the validity of the trial by introducing a bias. Therefore, treatment assignment should be made only after participants have consented to take part in the trial. The baseline data is collected after registration of the patient and before the treatment-allocation. **The investigator should not know the order of the treatment assignments in advance and should not be able to predict the treatment for the next patient to be enrolled.**

In an unblinded trial with a fixed block size the last allocation may be predictable since earlier treatment assignments are known. This is prevented by concealment of the treatment allocation by not revealing the block size and/or varying the size (e.g., AA BB; AB BA; BAB ABA).

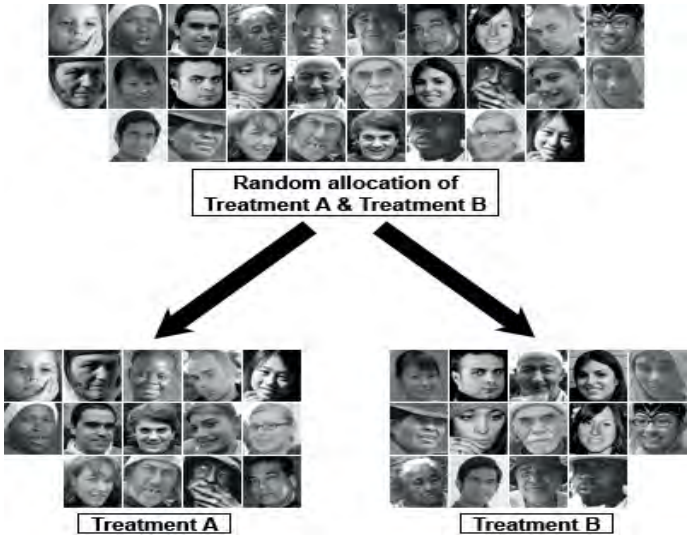
## Blinding

The question to ask is: were the patients, investigators and evaluators of the trial all blinded to which intervention patients received?

After random allocation of the intervention, the patient and/or the study investigators and/or the assessor of the outcome often do not know what treatment the patient was assigned. This is considered as masking or blinding (since the Ophthalmology society has an issue in using the later terms in a casual discourse or area other than their field of interest). This is central tenant of clinical trial research as knowledge of which treatment was received could influence the results through biased patient care (for example, giving add on therapies or supplementary treatment that itself might influence the outcome), biased measurement of outcomes or biased reporting.If only one of these three groups of people (patient, care-giver or assessor) are blinded it is called single blinding. If more than one of these groups are blinded it is called double blinding. There are, however, no universally accepted definitions of these terms. For some trials the classification is clear, but for others it is not simple.

## Similarity of the groups at baseline

An important aspect to report and read in clinical trials is that the intervention and comparison group should be **similar at the start** of the trial. If randomisation has been carried out properly, treatment groups should be similar in their baseline characteristics (generally given as Table 1). Baseline data collected from all participants may include data on demographic variables (such as age, sex, ethnicity, occupation, education), as well as other factors pertinent to disease course or episodes of illness. These data should be collected before random allocation, so that the data cannot be influenced by knowledge of the treatment group. Some small differences between groups in baseline characteristics may occur due to chance. However, any




large and important differences between groups at baseline may be evidence that the randomisation was not carried out properly.

## The Trial Conduct

An important aspect of the trial, after the design issue, is the conduct of the study. One has to keep in mind that clinical trials are more like a longitudinal studies, that too with an active experimentation. One of the biggest issue with the longitudinal studies is participants drop out. Similarly, completeness of follow-up is an important bench mark in the quality of the study.

**Was the conduct of the trial valid?**

- How complete was **follow-up** of patients in each group?
- Apart from the intervention(s) itself, were the groups treated equally?

## Question to ask:

- How complete was follow-up of patients in each group?

Over time, some of study participants will drop out of a trial and are no longer followed-up. It is common for losses to follow-up to increase over time, particularly if the follow-up period is long or if there are invasive procedures (such as blood sampling). When either the numbers of drop-outs or the characteristics of those who drop-out differ between groups, this is likely to result in (post-randomisation selection) bias, especially as the total numbers drop out increase.When we critically appraise the paper for the completeness of follow-up, following three questions should be answered:

- Was everyone in the trial described and followed-up?
- If not, were the numbers lost similar in each group?
- Are types of loss likely to be similar in the groups?

## Question to ask:

- **Apart from the intervention(s) itself, were the groups treated equally?**

When conducting a trial, it is important to treat each group equally, in terms of frequency and timing of follow-up done on the participants. The investigations carried out to assess the outcome or any adverse effects of the interventions should also be the same for both the groups. Additionally, supplementary treatment, if/when used should also be the same in both the groups if post-randmoisation bias is to be avoided.

If each group is treated equally, then results can be attributed to the intervention, and not to differential treatment of patients or ascertainment of the outcomes or alteration of the effect by other treatments. It is practical to treat each group equally in a trial if study investigators and those evaluating the trial remain blinded to treatment allocation. However, it may be difficult to maintain blinding throughout the trial if the intervention is associated with characteristic side effects, for example, some drugs cause extra-pyramidal side effects or others might change the color of urine which might be conspicuously noted in a cross over trial where each patient acts as his own control.

## Analysis of the Trial

The questions to ask was the analysis of the trial valid. The key to having a correct answer is to look at the groups and find out if the patients were analyzed in the groups to which they were randomised? When analyzing trial data, it is important to include all randomised patients (when possible) in the analysis. In addition, the primary comparison for most trials should be to analyze patients according to the treatment group to which they were randomised. This is irrespective of whether they underwent the intended intervention or whether they continued therapy according to the protocol stipulations. This is called **intention-to-treat analysis**. The other thing to look for was the statistical analysis pre-specified and appropriate, and could other outcomes have been measured but not reported? 'Looking for a pony' is a type of sub-group analysis in which investigators torture the data to a point that a significant "p" value is achieved in one of the sub-group analysis. This post-hoc analysis is generally discouraged unless specified in the protocol for certain high risk groups.

Trial data can be analyzed in many different ways. For example, we can:

- Analyze final values
- Analyze changes from baseline to final values
- Analyze final values adjusted for baseline values
- Use parametric or non-parametric tests
- Use transformed data (taking logs, for example) or untransformed data.

Each of these analyses might give slightly different results. The danger of this is that unless specified in advance what to report, the researcher is tempted to pick the most interesting result for acceptance of paper in a peer reviewed journal, or the one that is most favourable to the interests of the sponsor. In all fairness to researchers it may be difficult to specify the analysis methods in great detail as assumptions for specific statistical tests (for example, assumption of normality) may not come out to be true. However, an analysis plan should specify the rules by which alternative analyses are chosen. There is a move among academics to either have the trial protocol published or deposited with a journal prior to trial completion. This is done in part to avoid this type of bias in reporting of analyses. The pharmaceutical industry is heavily regulated and has to supply protocols to regulatory authorities prior to the trial being started - these protocols may have a detailed analysis plan included. In recent times it has been made mandatory to have trial registered with regulatory authorities or WHO which also require a plan

## What are the Results?

The most important part of the clinical trial reading or reporting is what the results are? This question is made up of two parts:

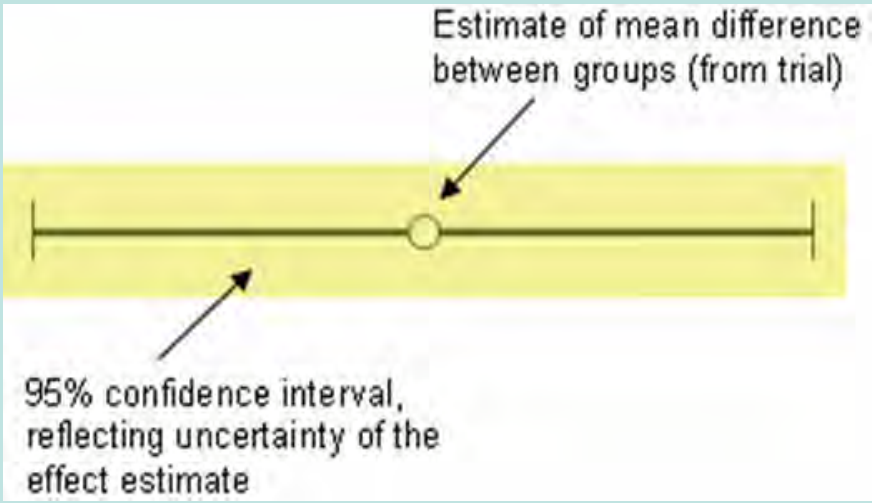
- How large was the effect of the intervention?
- How precise was this effect estimate?

## How large was the effect or effect size?

There are many ways in which treatment effects of binary outcomes can be presented. One of the most common is an **absolute** difference or risk difference. The other is the relative difference which is reported as odds ration or risk ratio. The third way can be a relative risk difference or a percentage of risk reduction. Many papers report the results in terms of a percentage reduction. For a relative reduction it is helpful to know what point the reduction has started from, and the actual data should always be provided. These decisions are as much based on the statistical design of the study as well as the stakeholders who are going to use this data for programmatic evaluation. Treatment effects of continuous measurements are usually analysed as absolute differences.

## How precise was the effect estimate?

When clinical trial are carried out, results are an **estimate** of the effect measure. This is because a study population is a sample of the underlying population.




Many different effect estimates could be obtained from other, equally plausible, random samples from the same underlying population. As a result of this potential sampling error, we want to provide some measure of uncertainty around our observed effect estimate, to indicate where the true value is likely to be. A '**confidence interval**' reflects the uncertainty of a point estimate, and will be wider with smaller sample sizes.

There are other types of inferences that can be made – for example, to what extent a hypothesis is supported by the data (using p-values). A **p-value** on its own can only tell us the strength of the evidence against the null hypothesis of (often) no difference/no relative difference. However it cannot tell us in which treatment group the benefit is seen, what the estimated size of any benefit is or how uncertain we might be in respect of this estimated effect.

So, the main results from a trial are best presented in terms of some treatment effect together with a confidence interval and (usually) a p-value. P-values on their own is misleading - they may reflect statistical significance but provide no measure of clinical importance. Journal editors and reviewers increasingly request on reporting of the 95% CI. In a final analysis if a trial reports no effect of an intervention, this may be because there is no true effect in the underlying population from which the study population was taken. Second inference can be there is a true effect, but bias in the design, conduct or analysis of the trial has masked this effect. Corollary to this is that the study sample size was too small to detect an effect (the study had low power).

Unfortunately many trials are too small and, as a result, will be unable to provide reliable answers to clinically meaningful questions. It is essential when planning a trial to calculate a sample size that will be sufficient to detect a clinically important effect with a specified power and level of significance. The sample size calculation should be reported when writing the trial, so that the reader can assess to what extent negative findings could be attributed to insufficient study power.

# RESPONSIBLE REFERENCING

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The word reference is derived from number of words derive from the same root, including refer, referee, referential, referent, referendum.[1] Referencing is an integral part of scientific research, writing and publication. Referencing allows tracing the sources of accessible, documented evidence. It helps to expand and spread the web of knowledge, guiding readers, reviewers and editors to the original work for critical scrutiny and verification of the research questions, the methods used to obtain the results, and discussions to compare and contrast with the available literature. [2]

Copying other's ideas and works without proper acknowledgements of source is a serious misconduct, plagiarism, and a fraudulent practice. Evidence based medical science involves detail description of ideas, its origin and development; by whom, when, where, why, how etc. [3] Referencing helps in advancing the knowledge base, either in agreement or counter agreement.
Some of the important reasons to cite references include:

- to acknowledge others work
- to give credit to the original source of work
- to direct readers to the original source of the information
- Add credibility to one's own work.

The issue of 'when' to reference is not so straight forward either. The common knowledge shared in the public domain, undisputed facts freely and publicly circulating may not require citation, for example, sun sets in the west, and other information freely shared by community and society. However, the complexity is that not everyone in a particular discipline or from different socio-culture background agree on what is common knowledge. Thus at times the simple logic is "if in doubt cite'.

Failure to 'cite' is cheating, which may be either intentional or unintentional. [5] The accuracy of content cited must match the content in the reference. Citation based on title and abstract, without reading the original article for the details of design, and process of their findings may result in errors and it is irritating when one cannot find the information in cited reference. [6] Authors, editors, reviewers should not use references to promote self-interests, and commit a misconduct of 'self-citation' which may become 'self-plagiarism'.
Scientific writing is an essential component of medical curriculum, and understanding various referencing systems is necessary for effective use of these tools. [7]Rapid growth of science has led to proliferation of scientific journals contributing to medical literature. With various referencing styles, manually referencing is labor intensive. Referencing soft wares have advanced overtime. Proper referencing is expected to demonstrate that one has read and researched for precise ideas from traceable sources. The list of references has an effect on overall work for possible academic debate and follow-up. [8] Scientists as authors produce references, and as readers and reviewers, they assess and evaluate references. Through this symmetrical relationship to literature, all scientists share, and take responsibility for tying together all knowledge contained in the ambit of their domain. Producing and evaluating references are, however, distinct processes, warranting different responsibilities.

The references should be provided with standard identifier (PMID PubMed ID, DOI-

digital object identifier), or other 'links' like 'GoogleScholar', Weblinks, etc. Accuracy of citations and references should be verified, ideally by electronic search.
There are several free reference management softwares available, few examples –

i. Zotero (https://www.zotero.org)
ii. Mendeley (https://www.mendeley.com)
iii. EndNote (https://endnote.com)

The referencing should include original publications. The quality of citations are mainly the 'validity of sources' and 'errors in citation' style. There are many referencing styles, but can be broadly categorized in to two types:

i. in-text author name (for e.g. American Psychological Association APA and Harvard style, used mostly in social science)
ii. Numerical citation (e.g. Vancouver style, common in scientific, medical journals).

Vancouver style is popular because it is friendly to author, reviewer, editor and librarian. References are numbered in Arabic numerals (after full stop in superscript in consecutive order in which they appear in the text, tables, and graphs and are listed at the end of document as 'references'. The Vancouver referencing style has been adopted by majority of biomedical journals. [4]

Some of the developing concept and useful tips for referencing include:

In Vancouver style referencing, the author/s are traditionally listed as proposed by western culture- "family space name full stop. However, as publication from Asian culture, especially Chinese (who write their name starting with family name first), now constitute significant proportion in the online literature, seems logical to write the authors name in full as it appears in their respective culture). Up to six authors, all are listed, in case of more than six, list first six and then use et al. Some journals have et al after three authors. Provide standard identifier of the manuscript, for example; digital object identifier (DOI), PMID (PubMed ID), PMCID (PMC ID), GoogleScholar, Weblink, etc. For style of referencing it's easier to search on google scholar and find the citation style by clicking on < " >, https://scholar.google.com

Journals and funding agencies are increasingly demanding to provide the Open Researcher and Contributor ID (ORCID), https://orcid.org/

Academia and universities around the world require that their graduates write and publish in scientific journals.

\Therefore, there is need to introduce courses and trainings in curriculum to develop the culture of research, writing and publications.

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## Ten rules for responsible referen cing are[9]:

1. Include relevant citations: All scholarly writing requires a demonstration of the relevance of the posed question, a display of the methods used, a rationale for the use of materials, and a discussion of issues relevant to the content of the publication.
2. Read the publications you cite: citation is not an administrative task. A single paper can be cited for multiple reasons, ranging from reported data to methods, and can be cited both positively and negatively in the literature. The only way to identify whether its content is relevant as support for your claim is to read it in full.
3. Cite in accordance with content: If you have decided that a specific study merits citation, the issue of specifically how and where to cite it, deserves explicit consideration.
4. Cite transparently, not neutrally: Citing, even in accordance with content, requires context. This is especially important when it happens as part of the article's argument. Not all citations are a part of an article's argument. Citations to data, resources, materials, and established methods require less, if any, context.
5. Cite yourself when required: In the context of critical discussions of citations and evaluations of citation-based metrics, self-citation has almost become a taboo. It is important to realize, though, that self-citation serves an important function by showing incremental iterative advancement of your work.
6. Prioritize the citations you include: Many journals have restrictions on the number of references authors are allowed to include. The exact number varies per publisher, journal, and article type and can be as low as three to as many as >100. Even if no reference limit exists, journals impose a word limit that includes references, effectively also capping the amount of references.
7. Evaluate citations as the choices that they are: Research publications are not mere vessels of data or findings. They convey a narrative explaining why questions are worth asking, what their answers may mean, how these answers were reached, why they are to be trusted, and more.
8. Evaluate citations in their rhetorical context: Rhetorical strategies serve to convince and persuade. Narratives are but one of the tools that can be used to persuade audiences. Metaphors, numbers, and associations, all feature in research papers as tools to convince our readers. The genre of the scientific article has had a century or more to evolve to incorporate many of them, with the goal of convincing readers that the author is right.
9. Evaluate citations as framed communication: Authors use words to accomplish things and, in service of those goals, position their work and that of others. They frame prior work in a very specific way, supporting the arguments. The positioning of X, Y, and Z either as the norm or as exceptions, as shown in Rule 8, is an example of framing. It is important to recognize such framing and that X, Y, and Z acquire meaning in the text as the result of the frame.
10. Accept that citation cultures differ across boundaries: Despite critiques of the system, science is organized in such a way that citations continue to act as a currency that is represented as universal. However, citation practices are, for the most part, local practices, whether local to laboratories or department or local to disciplines. When reading a paper from an adjacent discipline, respect its different norms and conventions for responsible referencing and proper citation.

SOUL@DUHS

# Newsletter & Magazine

# DRUGS IN THE VIEW OF C. G. JUNG

**Marie-Louise von Franz**
*Psychotherapist*

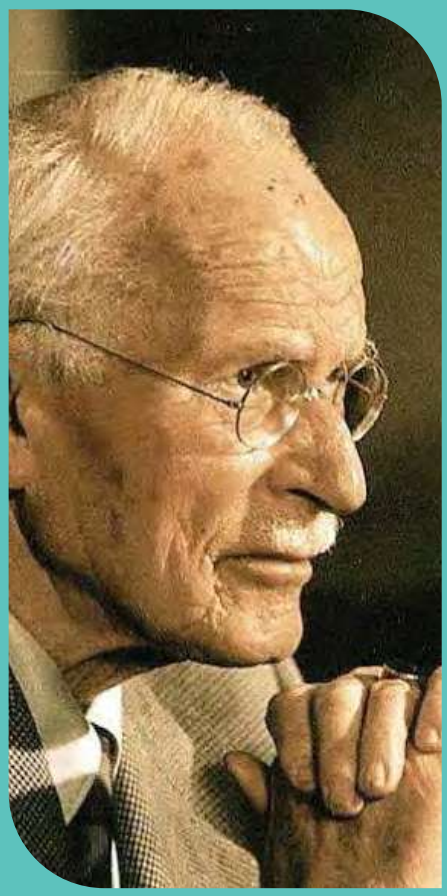
The flood of drugs that is rolling over our world today was not yet widespread at the time of Jung's death. Jung therefore was only familiar with the effects of mescaline (especially through Aldous Huxley's description) and only knew that such pharmaceuticals were beginning to capture attention in psychotherapy. He admitted in a letter of April, 1954 that he was not sufficiently acquainted with the psychotherapeutic value of such drugs for neurotic and psychotic patients to be able to form a conclusive judgment. He was profoundly disquieted, on the other hand, by our modern tendency to exploit such discoveries out of idle curiosity, without recognizing the growing moral responsibility that we incur:

'This is really the mistake of our age. We think it is enough to discover new things, but we don't realise that knowing more demands a corresponding development of morality. Radioactive clouds over Japan, Calcutta, and Saskatchewan point to a progressive poisoning of the universal atmosphere. . . .I am profoundly mistrustful of the "pure gifts of the Gods." You pay dearly for them'.

Drugs (hashish, mescaline, LSD, opium, heroin), generally speaking, bring about a decay of apperception, that is, a decomposition of the conscious synthesis and perception of gestalts (in the sense of Gestalt psychology), and thus cause the appearance of the normal perceptual variants—innumerable nuances of form, meaning, and value—that normally remain subliminal. This means above all an enriching of consciousness. We come into contact with "the sphere where the paint is made that colours the world, where the light is created that makes shine the splendour of the dawn, the lines and shapes of all form, the sound that fills the universe, the thought that illuminates the darkness of the void." This is an experience of the collective unconscious. If this experience were to be a God-given gift without a hidden counterpoison, then it would mean a tremendous enrichment, an expansion of consciousness by which we are naturally fascinated. But it is just this expansion and enrichment of consciousness that make integration and moral processing of what we see and hear in this state impossible. Therefore Jung says: "If you are too unconscious it is a great relief to know a bit of the collective unconscious. But it soon becomes dangerous to know more, because one does not learn at the same time how to balance it through a conscious equivalent. . . There are some poor impoverished creatures perhaps, for whom mescaline would be a heaven-sent gift without a counterpoison."

The world of the collective unconscious, which Jung, without drugs, was the first to discover in its essence as the primordial creative ground in every human being, is something alive that does not allow itself to be subjugated without an equal reaction. For this reason I have been occupied for a long time with the question of how the unconscious itself reacts to the taking of drugs. What do the dreams of addicts have to tell us about this problem? A young man, for example, who was a heroin smuggler and also frequently took LSD had the following dream:

I am in Tahiti on the sun-bathed beach. I have built myself a little straw hut under the palms and live by fishing in the sea. It is magically beautiful. Suddenly a tremendous storm tide comes and washes everything away. I am sucked under water and find myself suddenly in the depths of the sea, standing in front of a big writing desk at which the "Lord of the Sea" is sitting. He is a giant man-o'-war jellyfish who looks at me angrily, and it dawns on me that he is the one that sent the storm tide. "Yes,"



says the man-o'-war, "I am angry at you and am going to completely destroy you." Then I wake up with a shock.

The magical, primitive land of innocence amid the paradisiacal beauty of nature with its happy life, devoid of responsibilities—that is what the drug user really is seeking. He is alone there, without social or emotional human obligations. Earlier on, it was military deserters in our culture who actually did flee to such countries in reality. However, the "Lord of the Sea" is infuriated about this. The big, round man-o'-war is what Jung described as a mandala, a symbol of the Self, that is, of the ultimate regulatory transpersonal inner-psychic center. And this divine soul guide is angry at the dreamer and wants to destroy him. Thus the unconscious reacts negatively to the

irresponsible penetration into its sphere. And in fact, soon after this the dreamer went to pieces and was lost.

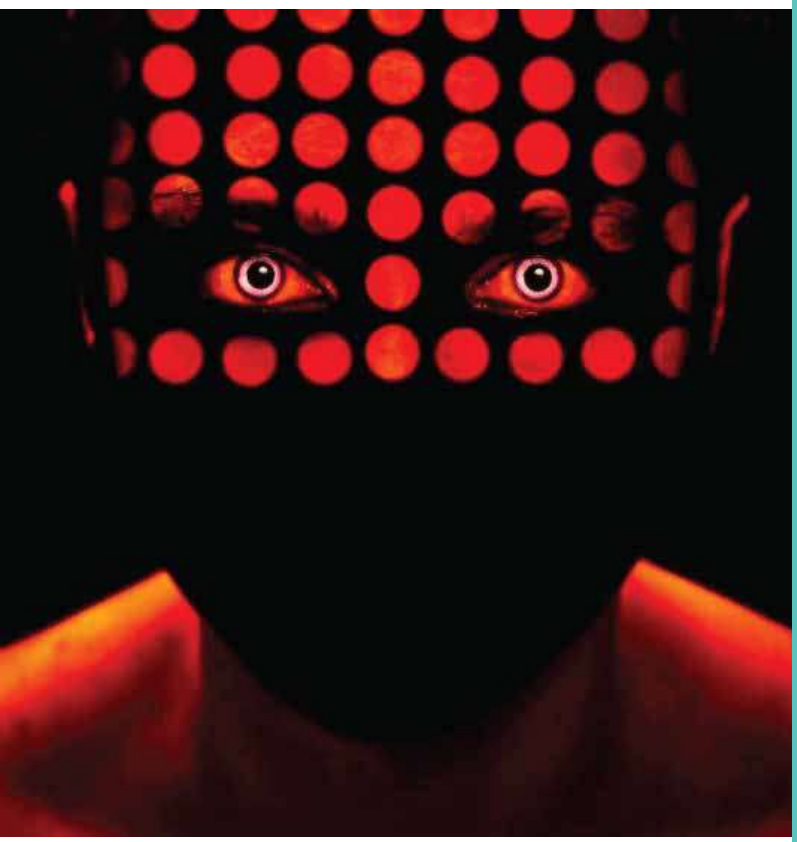
In another case, a slightly different picture emerged. A young man, who came from a ghastly family situation, was regularly taking LSD. He was perhaps one of those "impoverished creatures" mentioned by Jung for whom the drug contained no counterpoison. In any case, he always had a "good trip" with apparently no unfortunate consequences. But since this, nevertheless, did not solve his problem, he decided to undertake analysis, which guided him gradually and responsibly to the world of the beyond. At that point, he decided to take LSD again. He not only had a "bad trip" with psychosis-like anxiety states, but he was left from this trip with a nervous twitching of the head that lasted for months and frightened him a great deal. Evidently drug trips had now somehow become illegitimate, now that he knew of a better path to the unconscious. And the unconscious itself beneficently frightened him off. He never took LSD again, but he developed inwardly in a very rewarding fashion and turned himself toward life.

In a further case, a slightly different picture emerged. The person in question here was a young woman who was highly gifted artistically but had been greatly restricted psychically by an inculcated conventional outlook. Once, out of curiosity, she took LSD. After this, she dreamed that she had had a lovely trip but now she had to adopt a different approach. She saw her analyst standing in front of her with a playful-looking fool's cap on. The unconscious was obviously saying to her that she needed more creative "tomfoolery" and should acquire this through analysis (that is the reason why in her dream it was the analyst wearing the fool's cap), not only through drugs. The drug had indeed opened up to her the realm of unconventional experience, but now this had to be consciously and morally followed up.

Jung writes in the same letter cited above: ***'I only know there is no point in wishing to know more of the collective unconscious than one gets through dreams and intuition***. The more you know of it, the greater and heavier becomes your moral burden, because unconscious contents are transformed into your individual tasks and duties as soon as they begin to become conscious. Do you want to increase loneliness

and misunderstanding? Do you want to find more and more complications and increasing responsibilities? You get enough of it... This is not the point at all, to know of or about the unconscious, nor does the story end here; on the contrary it is how and where you begin the real quest.

And finally, here is the dream of a young user of hard drugs:
I am in a rowboat alone on the sea. The sun is shining brightly, and the surface of the sea is completely covered with magnificent flowers exuding a wonderful overpowering scent. I dip my arm in the water, and when I pull it out again, to the point it had been stuck into the water, it has disappeared! It has been eaten away by the water and is no more than a stump! As I look at it in terror, my boat capsizes and I awaken with a cry of fear. The dreamer had gone out onto the sea—into the collective unconscious. The magnificent flowers symbolize the beauty and sweetness of the drug experiences. "Morphine gives me such sweet dreams," he would often say. But—and this is what the dream showed him—behind that lurks deadly decomposition, an annihilation of the personality and of life!



That the drug experience is a substitute for a Dionysian experience of the Divine is generally accepted today. The Christian image of God has lost its effectiveness for many people, and in this way the objective psychic intensity or energy that was formerly invested in it has become free. "God" is no longer to be found outside. Through our scientific intellect, we have divested the external world of its soul. Jung, however, stressed that this has certain psychological consequences:

'The materialistic error was probably unavoidable at first. Since the throne of God could not be discovered among the galactic systems, the inference was that God had never existed. The second unavoidable error is psychologism: if God is anything, he must be an illusion derived from certain motives—from the will to power, for instance, or from repressed sexuality.' Through this, the person for whom "God is dead" will usually immediately fall victim to inflation, that is, end up in an overblown dissociated state in which he feels himself to be the "new God," as the example of Nietzsche shows us. Or else he will be overrun by some urge or craving, one that will now exhibit the same intensity as the image of God had done previously.

Here it must be mentioned that intoxicating substances are not the only dangerous addiction of our times. Another dangerous form of addiction is ideological possession, which can make the individual just as "drunk," puffed up, and dissociated as a drug, and in addition misleads him into wanting to impose his ideas on society through force. The energy that previously was invested in the idea of God is poured into the ideological, political, or sociological doctrine, which is then fanatically believed in. It is usually the extravert who has recourse to this form of intoxication, whereas the introvert prefers to pursue inner images with the help of drugs. The danger in both cases lies in the lack of spiritual freedom of the individual who is overrun by overwhelming unconscious fantasies. Jung says: The strongest and therefore the decisive factor in any individual psyche compels the same belief or fear, submission or devotion which a God would demand from man. Anything despotic and inescapable is in this sense "God," and it becomes absolute unless, by an ethical decision freely chosen, one succeeds in building up against this natural phenomenon a position that is equally strong and invincible.

***'This counterposition would correspond to a free choice through a moral decision in favor of a spiritual God who is experienceable within one's own psyche. "Man is free to decide whether "God" shall be a "spirit" or a natural phenomenon like the craving of a morphine addict, and hence whether 'God' shall act as a beneficent or a destructive force." This God would be that ultimately unknown something that Jung calls the Self. Serving it does not amount to egocentricity, but, on the contrary, is a self-limitation through which inflation and dissociation can be avoided. Serving the Self is a long, hard labor on oneself, but one which is rewarding, for the inner richness of the psyche that reveals itself through this is the only possession in this uncertain world that cannot be taken away from us. Mankind often proceeded to new realizations by passing through errors. It seems to me very understandable, and more than pardonable, if many people in the younger generation are unable to bear the intellectual vacuity and soullessness of our technical nonculture and therefore have recourse to drugs. But then for every individual the hour of destiny strikes in which he must decide whether he wants to sink forever into this meaninglessness, or pass through it as through a gate and go on to the great work of objective self-knowledge.'***

# THE DARK NIGHT OF THE SOUL

Editorial Team

Mystics and ancient clergies have talked about the Dark Night of the Soul throughout history. But it was John of the Cross, a Carmelite priest, who wrote a poem called the Dark Night of the Soul (Noche Oscura). In Noche oscura, a young girl (the soul) narrates an adventurous escape to meet her lover (God). In Llama de amor viva the soul addresses her lover (God) and recreates the state of ecstatic union she experiences when with Him. **La noche oscura. Dark Night (of the Soul)**. Since then, the term became widely used to describe one of the spiritual awakening stages. The Dark Night of the Soul corresponds with seven stages of transformation which follow a near orderly pattern. Dark night of the soul corresponds to the stage 3 in the transformation journey. However, you can experience these stages even without going through the Dark Night of the soul.

The seven stages of transformation are:

**Stage 1:** Cry for help
**Stage 2:** The Initiation
**Stage 3:** The Dark Night of the Soul
**Stage 4:** Distant Dawn
**Stage 5:** Tapping into Purpose
**Stage 6:** Balance and Foundations
**Stage 7:** Inner Power

During the Dark Night of the Soul, something we identify ourselves with is taken away from us. It can be the death of someone we loved, a separation from a lifelong partner, meeting, and instantly losing the love of your life, an illness, or losing financial stability. It's like the ground shakes beneath our feet, and we don't know who we are anymore. The meaning of our previous life is gone. We feel that our identities and personalities are dying, one after another.

Unlike the depression, the Dark Night of the Soul is primarily an experience of our soul. And it's even more extreme because the vast majority of people aren't in a conscious relationship with their soul. Then the Dark Night comes, and they feel a sense of loss of something they hadn't known existed.

During the Dark Night of the Soul, your soul calls for your attention in the most sensitive spot. Slowly but surely, you're unplugging from the illusions of the three dimensional (3D) reality. By emptying yourself of the false beliefs, you're creating space for the new you. The new you is aligned with your soul and your higher self. As you start getting to the other side of the tunnel, something in you will guide you to embody your soul, and this is the beginning of self-mastery.

The mystics describe that your soul has always been calling you, but now you can't miss her cry anymore. For once, you can hear with your spiritual hearing. You're returning to your true origin, which is love.

What happens after the Dark Night of the Soul is up to you. Some people continue to deepen their new-found sense of life and self. While some fear their experience and allow their fear to rule their lives once again. Yet, this time, they're aware of it.

Either case, after the Dark Night of the Soul, you'll continue going through spiritual tests and learning. Your soul will lovingly guide you to the next levels and push you to your limits again and again. Our being truly has infinite layers to which we're awakening. Spiritual evolution doesn't end here. Neither has it ended with enlightenment. Every layer has something to teach you.

The Dark Night of the Soul isn't the end. It's the beginning. You're born again.
SYLVIA SALOW

The "dark night of the soul" is a term that goes back a long time. Yes, I have also experienced it. It is a term used to describe what one could call a collapse of a perceived meaning in life…an eruption into your life of a deep sense of meaninglessness. The inner state in some cases is very close to what is conventionally called depression. Nothing makes sense anymore, there's no purpose to anything. Sometimes it's triggered by some external event, some disaster perhaps, on an external level. The death of someone close to you could trigger it, especially premature death, for example if your child dies. Or you had built up your life, and given it meaning – and the meaning that you

had given your life, your activities, your achievements, where you are going, what is considered important, for some reason collapses.

It can happen if something happens that you can't explain away anymore, some disaster which seems to invalidate the meaning that your life had before. Really what has collapsed then is the whole conceptual framework for your life, the meaning that your mind had given it. So that results in a dark place. But people have gone into that, and then there is the possibility that you emerge out of that into a transformed state of consciousness. Life has meaning again, but it's no longer a conceptual meaning that you can necessarily explain. Quite often it's from there that people awaken out of their conceptual sense of reality, which has collapsed.

They awaken into something deeper, which is no longer based on concepts in your mind. A deeper sense of purpose or connectedness with a greater life that is not dependent on explanations or anything conceptual any longer. It's a kind of re-birth. The dark night of the soul is a kind of death that you die. What dies is the egoic sense of self. Of course, death is always painful, but nothing real has actually died there – only an illusory identity. Now it is probably the case that some people who've gone through this transformation realized that they had to go through that, in order to bring about a spiritual awakening. Often it is part of the awakening process, the death of the old self and the birth of the true self.

The first lesson in A Course in Miracles says "Nothing I see in this room means anything", and you're supposed to look around the room at whatever you happen to be looking at, and you say "this doesn't mean anything", "that doesn't mean anything". What is the purpose of a lesson like that? It's a little bit like re-creating what can happen during the dark night of the soul. It's the collapse of a mind-made meaning, conceptual meaning, of life… believing that you understand "what it's all about". With A Course in Miracles, it's a voluntary relinquishment of the human mind-made meaning that is projected, and you go voluntary into saying "I don't know what this means", "this doesn't mean anything". You wipe the board clean.

You are meant to arrive at a place of conceptual meaninglessness. Or one could say a state of ignorance – where things lose the meaning that you had given them, which was all conditioned and cultural and so on. Then you can look upon the world without imposing a mind-made framework of meaning. It looks of course as if you no longer understand anything. That's why it's so scary when it happens to you, instead of you actually consciously embracing it. It can bring about the dark night of the soul – to go around the Universe without interpreting it compulsively, as an innocent presence. You look upon events, people, and so on with a deep sense of aliveness. You sense the aliveness through your own sense of aliveness, but you are not trying to fit your experience into a conceptual framework anymore.

**Eckhart Tolle**

# 12 RULES FOR LIFE: AN ANTIDOTE TO CHAOS BY JORDAN B. PETERSON

The constituent elements of the world are order and chaos, and not material things. Order and chaos are the yang and yin of the famous Taoist - just when things seem secure, the unknown can loom, unexpectedly and large. Conversely, just when everything seems lost, new order can emerge from catastrophe and chaos. For the Taoists, meaning is to be found on the border between the ever-entwined pair. To walk that border is to stay on the path of life, the divine Way.

The following rules will help people understand what they already know: *that the soul of the individual eternally hungers for the heroism of genuine being, and that the willingness to take on that responsibility is identical to the decision to live a meaningful life. If we each live properly, we will collectively flourish.*

## RULE 1 Stand Up Straight With Your Shoulders Back.

Attend carefully to your posture. Quit drooping and hunching around. Speak your mind. Put your desires forward, as if you had a right to them—at least the same right as others. Walk tall and gaze forthrightly ahead. Dare to be dangerous. People, including yourself, will start to assume that you are competent and able (or at least they will not immediately conclude the reverse).

## RULE 2 Treat Yourself Like Someone You Are Responsible For Helping.

Strengthen the individual. Start with yourself. Take care of yourself. Define who you are. Refine your personality. Choose your destination and articulate your Being. As the great nineteenth-century German philosopher Friedrich Nietzsche so brilliantly noted, "He whose life has a why can bear almost any how."

## RULE 3 Make Friends With People Who Want The Best For You.

It is not easier to surround yourself with good healthy people than with bad unhealthy people. A good, healthy person is an ideal. It requires strength and daring to stand up near such a person. Have some humility. Have some courage. Use your judgment, and protect yourself from too-uncritical compassion and pity.

## RULE 4 Compare Yourself To Who You Were Yesterday, Not To Who Someone Else Is Today.

Perhaps happiness is always to be found in the journey uphill, and not in the fleeting sense of satisfaction awaiting at the next peak. Be cautious when you're comparing yourself to others. You're a singular being, once you're an adult.

Set your sights on the betterment of being. Align yourself, in your soul, with Truth and the Highest Good. There is habitable order to establish and beauty to bring into existence. There is evil to overcome, suffering to ameliorate, and yourself to better.

## RULE 5 Do Not Let Your Children Do Anything That Makes You Dislike Them.

Clear rules make secure children and calm, rational parents. Clear principles of discipline and punishment balance mercy and justice so that social development and psychological maturity can be optimally promoted.

## RULE 6 Set Your House In Perfect Order Before You Criticize The World.

Don't reorganize the state until you have ordered your own experience. Have some humility. If you cannot bring peace to your household, how dare you try to rule a city? Let your own soul guide you.

## RULE 7 Pursue What Is Meaningful (Not What Is Expedient).

What is expedient works only for the moment. It's immediate, impulsive and limited. Meaning is what manifests itself when the many levels of being arrange themselves into a perfectly functioning harmony, from atomic microcosm to cell to organ to individual to society to nature to cosmos, so that action at each level beautifully and perfectly facilitates action at all, such that past, present and future are all at once redeemed and reconciled.

*Dr. Jordan B. Peterson is a clinical psychologist and professor emeritus at the University of Toronto. From 1993 to 1998 he served as assistant and then associate professor of psychology at Harvard. Dr Jordan Peterson penned the popular global bestsellers Beyond Order: 12 More Rules for Life & 12 Rules for Life: An Antidote to Chaos, #1 for nonfiction in 2018 in the US, Canada, the UK, Australia, New Zealand, Sweden, the Netherlands, Brazil and Norway, both translated into some 50 languages. The latter book has sold more than five million copies; the former, released in mid 2021, 750,000.*

**About 12 Rules for Life -**

*"Peterson invites his readers to embark on their own intellectual, spiritual, and ideological journeys into the many topics and disciplines he touches on. It's a counter-intuitive strategy for a population hooked on the instant gratification of ideological conformity and social media 'likes, but if Peterson is right, you have nothing to lose but your own misery."*

**James Grainger, Toronto Star**

## RULE 8 Tell The Truth- Or, At Least Don't Lie.

When the lies get big enough, the whole world spoils. But if you look close enough, the biggest of lies is composed of smaller lies, and those are composed of still smaller lies— and the smallest of lies is where the big lie starts.

To tell the truth is to bring the most habitable reality into being. Truth builds edifices that can stand a thousand years. Apprehend your personal truth. Communicate it carefully, in an articulate manner, to yourself and others. In Paradise, everyone speaks the truth. That is what makes it Paradise. Tell the truth. Or, at least, don't lie.

## RULE 9 Assume That The Person You Are Listening To Might Know Something You Don't.

Listen, to yourself and to those with whom you are speaking. Your wisdom then consists not of the knowledge you already have, but the continual search for knowledge, which is the highest form of wisdom.

## RULE 10 Be Precise In Your Speech.

Confront the chaos of Being. Take aim against a sea of troubles. Specify your destination, and chart your course. Admit to what you want. Tell those around you who you are. Narrow, and gaze attentively, and move forward, forthrightly. Be precise in your speech.

## RULE 11 Do Not Bother Children When They Are Skateboarding.

And if you think tough men are dangerous, wait until you see what weak men are capable of. Leave children alone when they are skateboarding.

## RULE 12 Pet A Cat When You Encounter One On The Street.

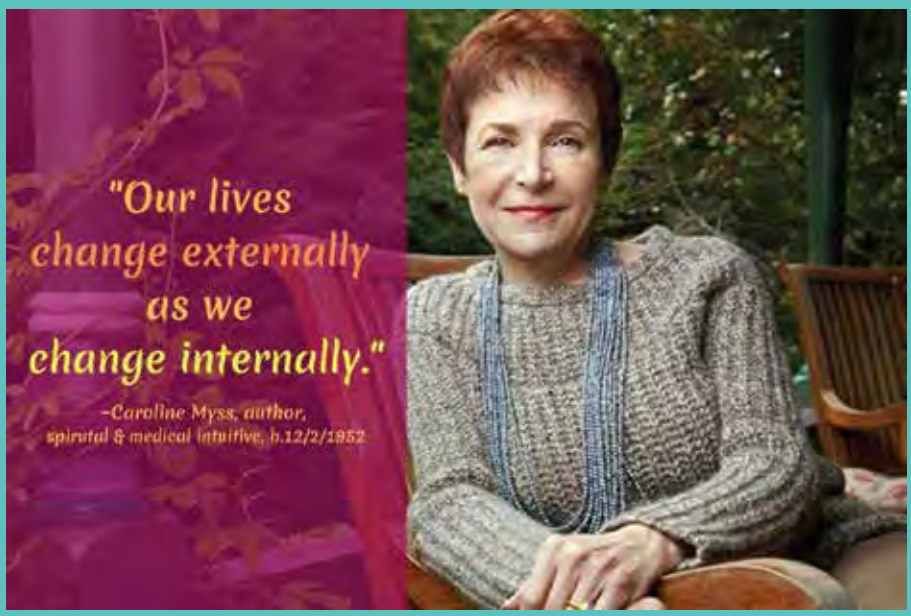
Cats are a manifestation of nature, of Being, in an almost pure form. Furthermore, they are a form of Being that looks at human beings and approves.

And maybe when you are going for a walk and your head is spinning a cat will show up and if you pay attention to it then you will get a reminder for just fifteen seconds that the wonder of Being might make up for the ineradicable suffering that accompanies it. Pet a cat when you encounter one on the street.

How do you build yourself into someone on whom you can rely, in the best of times and the worst—in peace and in war? How do you build for yourself the kind of character that will not ally itself, in its suffering and misery, with all who dwell in Hell? The questions and answers continued, all pertinent, in one way or another, to the rules outlined above.

# SPIRITUAL MADNESS:
## A MODERN MYSTIC JOURNEY THROUGH THE DARK NIGHT OF THE SOUL

Editorial Team




**What is spiritual madness and why must we endure so much on our journey to becoming conscious?**

In order to understand spiritual madness you have to start from a perspective as large as you can get which is '*for what purpose were you born?*'

In the mystical tradition when you would enter a monastic lifestyle you would prepare yourself to ask those questions. You would ask questions because mystics in ancient times knew that once direct contact with God is invoked everything in your life will turn upside down. The present human era has been given access to the interior of secret chambers that had been secret for almost two thousand years We think consciousness is the end of chaos; that to become conscious is to stop the flow of change but it's quite the opposite. In the journey of consciousness we invite god into our lives. When you start praying for spiritual intimacy you have to enter a journey of going into yourself alone- a journey of breaking your allegiance to human reasoning and entering into divine order versus human order. The whole purpose of a spiritual path is to transcend the need for human logic.

We are now living in a culture that is completely immersed in mysticism or we could say that mysticism has gone mainstream. When you look at the types of struggles people are enduring in their lives you recognize they don't need a therapist, rather they need a spiritual director and that we turn to therapists in lieu of spiritual directors because we don't have any.

In the contemporary mystical journey when people enter the vulnerable stage of separation, this is where depression comes and they begin to enter the first stage of madness. They have to begin the journey by seeing into whose hands they have commended their spirit other than God. In order for that to happen they have to experience the failure and breakdown of the human world.

This madness is necessary and is caused by that first feeling of being disconnected to the human world perceived through five senses. Then comes the separation process where they suddenly really realize that they don't trust this human order at all and their spirit actually begins to sort of detach from the life that they have been living.

It's a spiritual detachment not a physical one. They feel it physically. All of a sudden they feel almost like a stranger in a strange land. They walk the familiar roads of a town but they forgot how they felt about them; they can't seem to find their feelings for the things that are the most familiar to them.

That's where frightening things begin because they realize that they no longer know what schemata of order to trust since they can't trust physical order anymore.

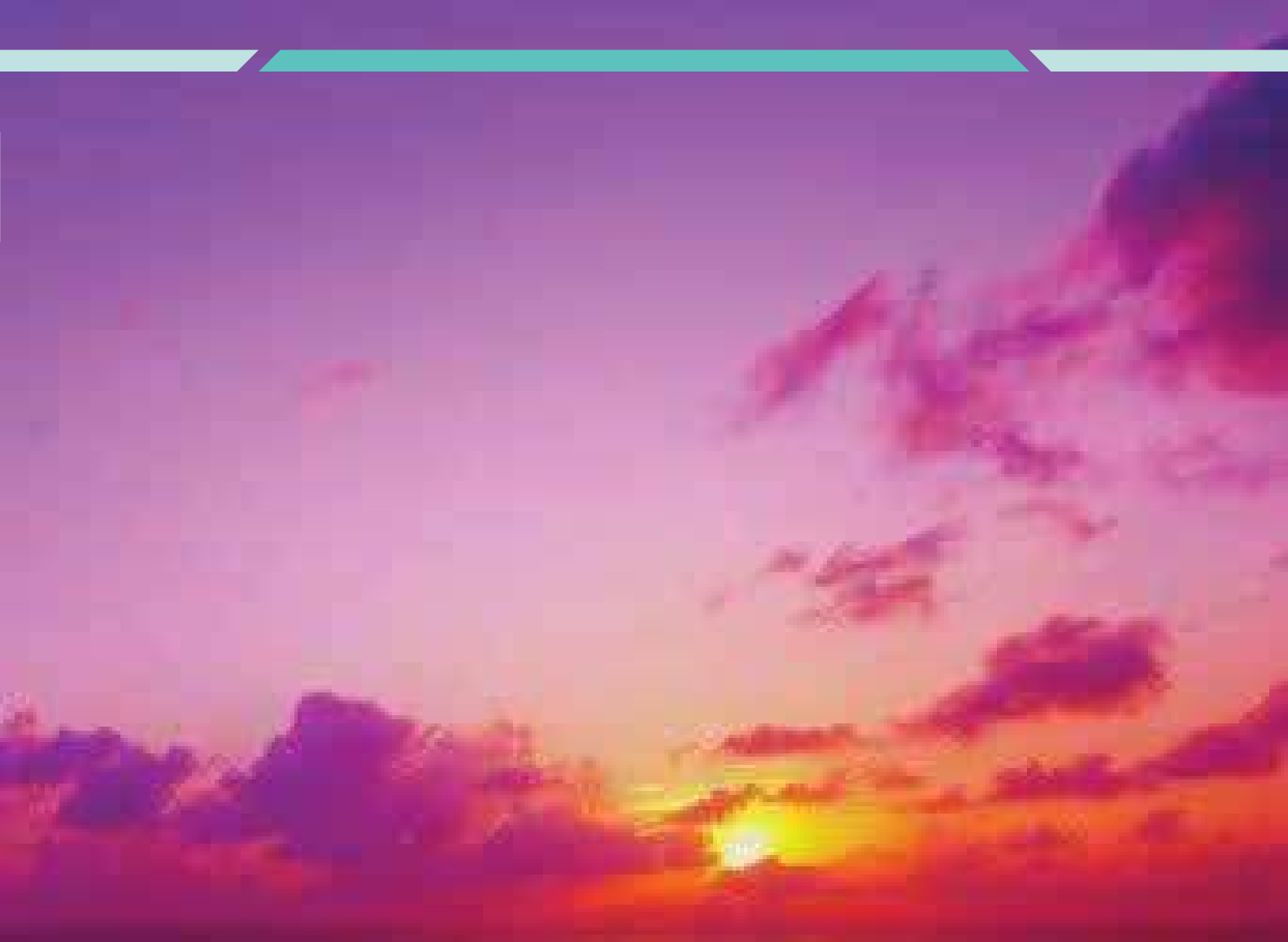
**You enter the classic dark night!**

People should wait for guidance and this is where stage two of guidance comes in. It may look like plain waiting initially like waiting for your ego to stop dictating your journey. Waiting to where it finally doesn't make any difference if you have to wait a lifetime.

Suddenly waiting is no longer a focus; suddenly you're unaware that you're waiting at all and you've arrived. What if you enter into the mystery to get you to begin to break the cycle of praying to God with expectations?! What if you're given a challenge, an illness, a difficult marriage and you have to endure?! And why do you have to endure?

Endurance gives you spiritual stamina. Spiritual endurance is about being alone since loneliness is observed to be bigger fear than the fear of dying.

And there are very few people who are genuinely on the mystical path and have



not been asked to endure aloneness. Why so? Because you must be able to wait for the voice of God .You have got to be able to say I have no attachment to fears and expectations anymore and then you have to be able to say what do you want from me?

It's the hardest thing to understand that the divine does not play by our rules. We are continually expecting Divine to operate by our reward and punishment system and human rules. At this stage you encounter your archetypal forces and you're unconscious to see what's been controlling you all these years. You're asking to see can I live and accept any order God gives me what if god said strip away everything you have and live on your own and I will take care of you as the ultimate trust act of whether or not you trust the presence of god in your life. You come face to face with the fact that you have a tremendous fear of being alone. You need to look at how that fear determines your prayers and the choices you make in your life and how you allow distractions to happen because you're afraid of being alone. You need to look at what being alone brings out in you. Does it make you depressed or feel unloved or make you unloving or make you begin to question there's something wrong with me. Whatever it makes you feel, enter in it with strength since there is where you find yourself studying your faith.

You must begin to realize by this stage that **you are incarnated to experience life patterns that will bring out the part of you that doesn't know God.** You will experience betrayals and all kinds of pain. They are not designed to hurt you but to bring out the part of you that doesn't know God. That part of you has authority over your soul and it demands *'you should have more out of your life than this', 'you should have it all'* .It's the part of you that talks to you in fantasy and is not authentic It has been seduced and you have to recover from seduction which is very painful because you feel betrayed; *but it's not God that betrayed you it's the way in which we've decided God should look.*

Ask yourself for what reason did I choose a spiritual path? Explore the fantasies that you have. The largest fantasy is that spirituality is the solution to chaos and chaos will stop with spiritual clarity. There's no truth to that at all. The truth is chaos, is clarity and therein lies one of the cores of the divine mind. You're learning a different level of power - the divine power and the way the divine orders and speaks through your life. You find yourself developing the sweetness of sight that allows you to recognize there's no

such thing as a small task if this is the task. III In practical life you may be given a task to care for a crippled relative or do some other work of service. You feel like your life is passing in front of you; when you feel like you are a creative person whose creativity is going unexpressed and you find yourself doing menial tasks to pay the bills. In these cases it's very hard to hold your center but there's great learning in them that is learning to trust. When you live in divine consciousness you live in the perspective that there's no such thing as an invisible act of power it's all visible to God.

There will be times when you're in madness; you won't be able to feel the thing for the person you think you love the most. There will be times when you won't be able to generate one ounce of sexual energy or one ounce of emotional energy. You will find yourself somehow drifting in this state of oblivion walking the streets thinking what do I do; how do I get out of this what have I done and you wait and you wait.

You then tell yourself: I am going through the breakdown of the way I want God to be, so I can allow God to be the way God needs to be in my life instead of the way I want Him to be. Another important truth is you can't make a wrong choice. It's not possible. You also can't miss your life's calling because no matter what you're living it's serving your life. If you said to God: all right balls in your court you tell me where you want me to live; you tell me what you want will do; half the madness is because you've invited God in on those terms and then you start dictating how you want God to answer your prayers. The path of mysticism is the path of release to an order that has no human order. This is where the ecstatic part begins when you go through the separation stage and you're into your sadness hang on. Tell yourself this is what I'm supposed to do. I need to detach. I need to keep myself centered and endure the madness.

Part of the reason you have to go through madness is because you've taken your earth ambitions and woven them into the way you think God is. We frequently find ourselves in this curious paradoxical crossroads - two paths that are incongruous operating inside of you simultaneously, one voice that says get ambitious you can do whatever you want and this other voice that says leave it up to me and release. How can you not be in madness with this type of dynamic going on?

We are carving a whole new path of contemporary mysticism that addresses the egocentricized people we've become. Our challenge nowadays is to merge what the psychotherapeutic world has awoken in us with what we want spiritually, which is intimacy with God.

It is essential that you take a look at what is ordinary self-esteem and you realize you're not just after therapeutic self-esteem (the ability to say no when someone's trying to get you in bed or the ability to tell somebody they offended you) but also spiritual self-esteem; spiritual self-esteem is the capacity to close your eyes and recognize 'I'm hearing guidance and I need to act on it immediately'. It is the capacity to maintain your **spiritual life in silence. Spiritual self-esteem in contemporary terms is the challenge of the release of the self to God while being strong enough not to release it to the physical world. As it goes we are meant to live in the world but not to become of the world.** In order to find ourselves with any kind of psychological peace we have to know that our journey is not to sell our soul. Spiritual discipline is the discipline of becoming honest. For this, find a spiritual mentor. Therapists have taken the role of healers but that is not sufficient. Everyone needs someone to discuss their incongruencies.

You have to be able to go to someone and say 'I'm working on forgiving and I can't do it, I haven't heard god for months ...How do i survive this?, I'm going through a cycle of madness my madness looks like this '.

Madness spiritually speaking repeats itself you don't only have one dark night it comes again. It comes when necessary and when you're in that dark night you need to have someone who can just sit there and listen to you scream: I am in darkness, I can't hear a thing. I don't know which way to go!

You need to have someone who says

*'When you are in darkness you are never more closely held ... you need to experience that paradox that God comes to you most clearly when you are most alone!'*. Hence again and again you're going to return to an ordinary life where you have families and children and jobs and simultaneously you're praying for divine clarity while living in a world of incredible chaos. To manage this it is important to articulate how you think the voice of god should sound to you? Where you're looking for that voice? What you think guidance should look like? How you think it should speak to you? ; *Because all the while God is talking to you, you may not be hearing it!*

Have the ability to enter chaos and see that as much part of God as tranquility. Also one must stop dividing his experience of god into pleasure and pain, chaos and stability instead live it in this point of view that I am always in touch with Him.

There would be a need to have someone who simply witnesses what you're going through, not explains it since the journey is not to find someone who can explain your mysteries but who can listen to them with you.

And when all of a sudden the light turns on and the darkness is over, don't expect the moment to be something profound like a vision; just expect the madness to stop. You may be living your ordinary life and then one day you realize that you don't feel lost anymore. You realize that the madness has stopped. You find yourself in a situation that three or four years ago would have scared you to death but doesn't scare you anymore. You think how come I'm suddenly okay: that is spiritual intimacy. There is a dialogue going on between you and God and it feels like okayness .

## WORLD MENTAL HEATH DAY – INEQUALITIES IN MENTAL HEALTH

Pakistan Institute of Living & Learning in collaboration with Ziauddin University and Dow University of Health Sciences organized World Mental Health Day seminar at Ziauddin Hospital KDLB campus to spread awareness about mental health issues and highlighted inequalities in mental health in Pakistan and globally – 10th October 21

## THE 7TH MEETING OF SENATE DUHS

The 7th meeting of senate Dow University of Health Sciences was held at Dow Campus on 24th November 2021 .

Vice Chancellor of Dow University, Prof. Mohammad Saeed Quraishy shared his vision in his welcome address. The meeting was attended by the prestigious professors and faculty of DUHS and chief guest Dr Azra Fazal Pechuho.

DUHS SENATE – November 21

## CLINICOPATHOLOGICAL CONFERENCE BY PSYCHIATRY DEPT. AT MUIN AUDITORIUM DUHS

Clinical case conference was conducted on 11th December 2021 by team of Psychiatry Department Dr Ruth K M Pfau Hospital Dow University in which issues related to consent and ethical dilemmas regarding interventions in psychiatric patients were highlighted in light of case history and recent evidences.


Department of Psychiatry, Dow Medical College, Faculty, Residents and Interns at Moin Auditorium after Clinical Case Conference.

## THE DOW UNIVERSITY OF HEALTH SCIENCES (DUHS) 11TH CONVOCATION

The Dow University of Health Sciences (DUHS) held its 11th convocation on Saturday at the Ojha campus, wherein a total of 3,179 graduates of year 2020 and year 2021 received their degrees in different disciplines, including medicine, dentistry, pharmacy, biotechnology, radiology, nursing and midwifery. Speaking at the ceremony, Sindh Governor Imran Ismail, also the university chancellor, asserted, "If someone can put Pakistan on the path of development, it is you. Continue to work hard and brighten the country's future," In her address, Health Minister Sindh Dr Azra Fazal Pechuho congratulated students and said, "The journey has just begun and you need to prove yourself on many fronts. Show the best of your abilities and never give up." DUHS Vice Chancellor Prof Mohammad Saeed Quraishy informed the audience about the university's progress over the years, and said it had been included in the top 400 universities of Asia

Faculty Department of Psychiatry DUHS Convocation 2021

## SUICIDE PREVENTION HELPLINE – A PUBLIC-PRIVATE PARTNERSHIP

Meeting with RUHBARU, NGO & SMHA for setting up a Suicide Prevention Helpline: Public-Private partnership – 24th December 2021

## OBITUARY -A MAN WITH VISION

Dr Tahir Shamsi (late) was not only a man with vision but also the one who had the courage to follow it . A man bigger than his rank and titles. I learned molecular biology and genetics from him while at AKU and subsequently started practice at NIBD afterwards. Life breathes easy, in the comfort of knowing, that clinicians like him existed. Also had the privilege of knowing the family. Truly wonderful people. May his soul rest in peace. (Professor Syed Haider Ali Naqvi ) Innalillahe wainna ellahe rajiun. A great noble visionary dedicated person worked for the betterment of those suffering. A great loss for Pakistanis. May Allah bless his soul with mughfirat (Associate Professor Aysha Serwat)

Late Professor Tahir Shamsi

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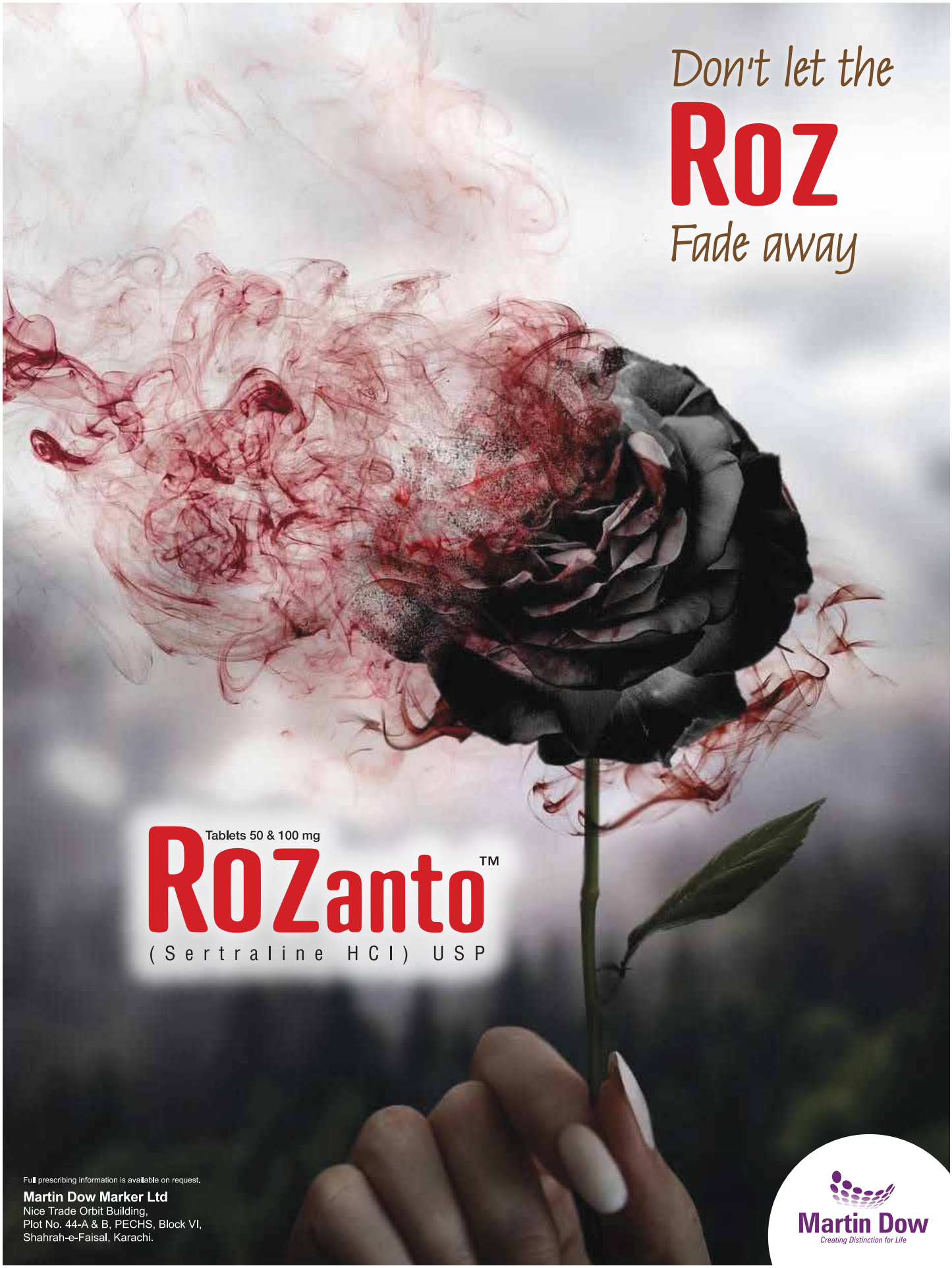
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