

Informed Consent in Biomedical Research: Scopes and Challenges

Abstract

Medical science is evolving constantly and this evolution cannot happen without biomedical research involving human participant. Owing to a tumultuous history, importance of ethical research cannot be over emphasized in today's world and the concept of informed consent becomes the guardian of ethics, not only to improve the bonding between the participant and researcher aiding a wholehearted involvement but also ensuring safety for the participants from research related injury/loss. Subject information sheet (SIF) and Informed consent form (ICF) are the fundamental elements of informed consent document. Process of obtaining them from illiterate and vulnerable populations involves the legally authorized representative (LAR) and impartial witness. Audiovisual recording becomes important in case of clinical trials. Process of obtaining informed consent becomes challenging for vulnerable populations as well as during pandemic situations. A comprehensive informed consent is essential for a credible and ethical research.

Keywords: Assent, consent, ethics, impartial witness, informed consent, legally authorized representatives

Prologue (Evolution of Informed Consent)

Advances in Medicine cannot be achieved without research involving human participants, but it is also of paramount importance that no harm is brought onto the research participants for the sake of research.^[1] Thus, it is required that the researchers obtain permission or approval from the participants to understand their willingness to undertake the risk onto oneself for the sake of benefit to the society which can be achieved by way of research. In other word, *consent* (meaning in Merriam Webster Dictionary “to give assent or approval” *verb*; “compliance in or approval of what is done or proposed by another” *noun*)^[2] becomes obligatory to ensure that *autonomy* of the patient is exercised. Autonomy is one of the primary pillar of ethics which decides research participants’ “right to self-governance, choice for care and the right to accept or refuse treatment;” and the only way to establish self-governance is to make sure that before expressing the willingness the participants have complete information about what to expect, the benefit/risk of the process, and the alternative options.^[3] Consent becomes

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futile if it's not complemented with detailed information regarding the entire research protocol in lay man's language (*vide infra*); thus, *informed consent* evolved as the guardian of medical ethics. What is true for research is true for routine medical practice and law-of-the-land all over has evolved with time from historically practiced “doctor-focused” approach to a more “patient-focused” approach.^[4] The history of medical research is marred with painful abuses, spanning nearly a century. Concept of “informed consent” is not just its outcome but has become an integral part of medical research to protect the interests of all the stakeholders. With advancements in understanding about pathogenesis, treatment, and various other aspects of different diseases and type of data being collected, the understanding of informed consent process undergoes a paradigm shift. The design of informed consent owes from tumultuous events in medical care and research involving human beings. A few historical landmarks with their repercussions are worth mentioning in this context

1. **The Duke of York's laws (1665):** Under this law, physicians and surgeons were required to obtain a patient's consent prior to treatment. The law also said

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- that as long as a treatment demonstrated no perceived risk or harm, physicians had the right to act without a patient's consent. The precise definition of harm was left to the judgement of the treating physician/surgeon.^[5]
2. **The Case of Pratt vs. Davis (1905):** A surgeon removed a woman's uterus and ovaries, without her knowledge, to treat her epilepsy. The court ruled in favor of the patient, arguing that a "Physician or Surgeon, however skillful [...] [cannot] violate without permission the bodily integrity of his patient."^[6]
 3. **The Case of Schloendorff vs. Society of New York Hospital (1914):** Upon accidental discovery of an abdominal mass, by physicians, in a woman complaining of stomach discomfort, the patient insisted against removal of that mass/tumor. But the physicians went on to perform a hysterectomy, followed by gangrene of her left arm because of surgical complications and some of her fingers had to be amputated. Additional surgeries for that hand had to be performed also because of an embolism from the original surgery. The verdict clarified that "Every human being of adult years and sound mind has a right to determine what shall be done with his own body [...]."^[7]
 4. **The Nuremberg Code (1949):** During the World War II, concentration camp victims were tortured and killed in the name of scientific research. The Nazi physicians, responsible for these heinous crimes, were tried by a tribunal of three American judges. They stated that "The voluntary consent of the human subject is absolutely essential." That research subjects "should be so situated as to able to exercise free power of choice," and that they "should have sufficient knowledge and comprehension of the elements of subject matter."^[8]
 5. **Declaration of Helsinki (1964):** Indirect influence of the Nuremberg code prompted the medical research community to frame its own guideline regarding behavior of researchers dealing with human subjects. These sets of guidelines by the World Medical Association has been the cornerstone of ethics in years to come and in its lifetime the "Declaration of Helsinki" has been revised many a times and has been constantly updated till October 2013. In most recent times, the area of ethical requirement in placebo-controlled trial and responsibilities of research participants at the end of study has been the focus of amendment.^[9]
 6. **The case of Salgo vs. Leland Stanford Jr. University Board of Trustees (1957):** The patient awoke paralyzed after a routine aortography, which proved permanent. The patient was never informed by the physicians and surgeons that such a risk even existed. The patient sued the hospital and was awarded \$250,000 in damages.^[10]
 7. **Stanford Prison Experiment (1971):** The researcher, Philip Zimbardo, at Stanford University indulged in an experiment, where a group of students were to act either as prisoners or guards in a makeshift penitentiary setting, leading to enduring psychological trauma for the participants.^[11]
 8. **Tuskegee Syphilis Experiment (1931-72):** In one of the most gruesome human experiments, effects of untreated syphilis were observed in poor African-American land workers for over 40 years by denying them an access to curative medicine. This monumental violation of human rights along with the Stanford prison experiment established groundwork for Federal policy for protection of human subjects, also known as the common rule.^[12]
 9. **Belmont Report (1979):** It defined the basic principles for oversight on research process, basic ethical parameters involving human subject research leading to creation of informed consent.^[13]
 10. **HPV vaccine trial (2007):** In India, HPV vaccine trial was initiated among tribal women (vulnerable population) under the pretence of "observational study" or "Demonstration project" without taking mandatory permission from Drug Controller General of India. The trial resulted in the death of seven girls and in 2010 the Indian parliament's standing committee on health observed that "safety and rights of those children were highly compromised."^[14]
 11. **Regulatory requirement for conduct of clinical trials in India (2013):** In the wake of public interest litigations, the Supreme Court of India recommended stringent control in the conduct of clinical trials to safeguard the rights of trial participants. Following the directions and observations of Supreme Court, the Central Drugs Standard Control Organization (CDSCO) introduced three steps to streamline the conduct of clinical trials. The institutions that are involved in reviewing and approving clinical trials were strengthened, the rights of clinical trial participants were protected, and measures were taken to reduce uncertainty and delay for clinical trial sponsors and investigators.^[15]

Definition of Informed Consent

It is the process by which a researcher/physician sensitizes a patient/participant about the nature of the study/research and what the patient/participant is supposed to go through (interventions and data collection) during the study/research, in their vernacular language that is non-technical and fully understandable by the patient/participant, in order to help them to participate with their complete willingness and without any coercion.^[16]

Consent in research and medical care

Elements of Informed Consent Document: For any modern-day research to be undertaken, a written informed consent is the most important pre-requisite that must be obtained in accordance with the Good Clinical Practices (GCP), the Indian Council of Medical Research (ICMR) guidelines, and the New Drugs and Clinical Trials Rules 2019.^[17-19] It is composed of "subject information sheet" and "informed consent form."

The Informed consent should highlight the Name of Investigator (s), Organization (s), Sponsors (in any), and the subject group on whom it is applicable.

1. **Subject Information Sheet (SIF):** The subject information sheet needs to be drafted in a lucid, non-technical, and simple language that can be easily understood by the participants. There needs to be an introductory section of the SIF where they need to be invited to the research and given the freedom to ask about their doubts (to the investigator or anyone they confide) and also to exercise their autonomy should they choose to participate. It is also required that adequate time be given to the participant to read the SIF, if necessary discuss it with their family/friends, and seek clarification of her/his doubts from the researchers before confirming their participation in the research.^[18]

The elements of SIF are as follows:

a. A statement that the study involves research: The SIF should clearly mention that the study is not a routine medical care to eliminate the perplexities that can shroud the mind of the participant with regard to “therapeutic misconception” (*vide infra*).^[1]

Example: “This Informed Consent Form is for men and women who attend clinic Z, and who we are being invited to participate in research on ‘X’. The title of our research project is “.....”^[20]

b. Explanation about the purpose and expected duration of the subject’s participation

Example: In a trial of new drug “*abc*” on urticaria. The SIF need to explain the disease in layman’s term (e.g. *wheals* or *hives*) with the details of the course of the medicine along with the number of visits to the clinic that will be required for the study.

c. Description of procedures to be followed and identification of any that are experimental

Example: “The participant has to take single tablet at bedtime for 6 weeks and record that in a daily diary that will be provided to him/her.” The mention of venipuncture for routine investigation before and at the end of the study should also be mentioned. If biopsies are necessary, then it is important to mention which would be the site of biopsy and whether anesthesia will be given or not.

d. Description of any foreseeable risk or discomforts to the subject, an estimate of their likelihood and a description of steps to be taken to prevent or minimize them. Unpredictable and/or serious adverse events are tricky matter and participants should be made aware about them too.

Example: The known side-effects are to be mentioned with the note that the side-effects are sometimes unpredictable and may vary from person to person in its seriousness. If a new side-effect is noted during the course of the study, the SIF should be updated accordingly (change of version). It is important

that the SIF should mention “We will follow you closely and keep track of any unwanted effects or any problems. We may use some other medicines to decrease the symptoms of the side effects or reactions. Or we may stop the use of one or more drugs. If this is necessary, we will discuss it together with you and you will always be consulted before we move to the next step.”^[20]

e. Description of any benefits to the subject or to others that may reasonably be expected from the research. However, monetary compensation is not a benefit. The benefit from the disease symptoms to be mentioned. Also a mention of the benefit to mankind for the development of new therapeutic option/understanding or diagnosis of a disease. It is noteworthy that monetary benefit is not accounted in the description since that will amount to coercion.

Example: “Any interim illnesses will be treated at no charge to you. If your child falls sick during this period, he/she will be treated free of charge. There may not be any benefit for you, but your participation is likely to help us find the answer to the research question. There may not be any benefit to the society at this stage of the research, but future generations are likely to benefit.”^[20]

f. Disclosure of any appropriate alternative procedures or courses of treatment that might be advantageous to the subject along with the description of “rescue medication/treatment” as appropriate for the condition. This is the most vital aspect of offering the “autonomy” to the participant to exercise his/her free will to choose between options available.

Example: The treatment options for urticaria need to be mentioned with a note that “If you do not wish to take part in the research, you will be provided with the established standard treatment available at the center/institute/hospital. People who have wheals/hives are given...”^[20]

The rescue treatment may be mentioned as “If we find that the medicine that is being used does not have the desired effect, or not to the extent that we wish it to have, we will use what is called a “rescue medicine.” The medicine that we will use is called QRS and it has been proven to control wheal/hives. If you find that the drug we are testing does not stop your wheal/hives and it is very uncomfortable for you, we can use the rescue medicine to make you more comfortable.”^[20]

g. Right to refuse or withdraw at any later date:

Example: “You do not have to take part in this research if you do not wish to do so. You may also stop participating in the research at any time you choose. It is your choice and all of your rights will still be respected.”^[20]

h. A statement describing to the extent of which, confidentiality of the records will be maintained,

including a description of who may have access to research records.

Example: “The information that we collect from this research project will be kept confidential. Information about you that will be collected during the research will be put away and no-one but the researchers will be able to see it. Any information about you will have a number on it instead of your name. Only the researchers will know what your number is and we will lock that information up with a lock and key. It will not be shared with or given to anyone except [name who will have access to the information, such as research sponsors, data safety monitoring board, your clinician, drug regulatory authorities, ethics committee members].”^[20]

- i. For research involving, more than minimal risk, an explanation and description of available compensation and medical treatments for research subjects if they are injured, where further information may be obtained and details of contact person in case of a research related injury.
- j. Information on the amount of remuneration/compensation, if any, to be provided to the subjects.

Example: “We will give you [amount of money] to pay for your travel to the clinic/parking and we will give you [amount] for lost work time. You will not be given any other money or gifts to take part in this research.”^[20]

- k. Special aspects of research which the participants are not familiar with have to be explained in details. These includes “Randomization,” “Blinding,” and “Use of Placebo.”

Example: “Because we do not know if the new anti-wheal/anti-hives drug is better than the currently available drug for treating wheal/hives, we need to compare the two. To do this, we will put people taking part in this research into two groups. The groups are selected by chance, as if by tossing a coin or decided by computer.

Participants in one group will be given the test drug while participants in the other group will be given the drug that is currently being used for wheal/hives. It is important that neither you nor we know which of the two drugs you are given. This information will be in our files, but we will not look at these files until after the research is finished. This is the best way we have for testing without being influenced by what we think or hope might happen. We will then compare which of the two has the best results.”^[20]

“A placebo or inactive medicine looks like real medicine but it is not. It is a dummy or pretend medicine. It has no effect on a person because it has no real medicine in it. Sometimes when we want to know whether a new medicine is good, we give some people the new medicine and some people the pretend or dummy medicine. For the research to be good, it is important that you do not know whether

you have been given the real medicine or the pretend or dummy medicine. This is one of the best ways we have for knowing what the medicine we are testing really does.”^[20]

- l. Details of contact person to answer pertinent questions about the research subject’s rights (Contact details for the research center’s patient representative and telephone number with email id)
- m. A statement that participation is voluntary and that refusal to participate or discontinuing participation at any time will involve no penalty or loss of benefits to which the subject is otherwise entitled^[21]

Example: “Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, all the services you receive at this clinic will continue and nothing will change. If you choose not to participate in this research project, you will offered the treatment that is routinely offered in this clinic/hospital for disease Z, and we will tell you more about it later. You may change your mind later and stop participating even if you agreed earlier.”^[20]

A very simplified acronym LASERS, although not exhaustive can summarize the important aspects of the information sheet, particularly useful for Dermato-surgical studies. It can be expanded as Liability waiver, type of Anesthesia, Surveillance, no Expectations/guarantee clause, Revocation of consent and Snapshots.^[22]

2. Informed Consent Form (ICF): It should be in accordance with the Appendix V of Schedule Y (Annexure III).^[23]

Practice of Obtaining Informed consent (with reference to Literate and Illiterate participant): A smooth informed consent process not only makes life easy for a researcher in terms of bonding with the participant and avoiding possible medico-legal confrontations but also ensures compliance and autonomy of the participant. The process can be simplified by following flow-charts as described in Figure 1 (for Literate Participants), Figure 2 (for Illiterate Participants), and Figure 3 (for both Illiterate Participants and Illiterate Legally Acceptable Representatives).^[16]

Introduction to Legally acceptable representative (LAR) and impartial witness: A LAR is an individual or a legal body authorized under applicable law to provide consent on behalf of a prospective participant, toward his/her participation in a research, under such a scenario where a participant is unable to give informed consent (e.g. minor, insanity, disability, unconsciousness). In case the participant or LAR are unable to read/write, an impartial witness must be present during the entire informed consent process and sign the ICF. It is important to understand that legally acceptable representative (LAR) is different from **Legally authorized representative**, who are chosen by applicable law or judicial authority. An impartial witness is any person who is independent of the research and cannot be unduly

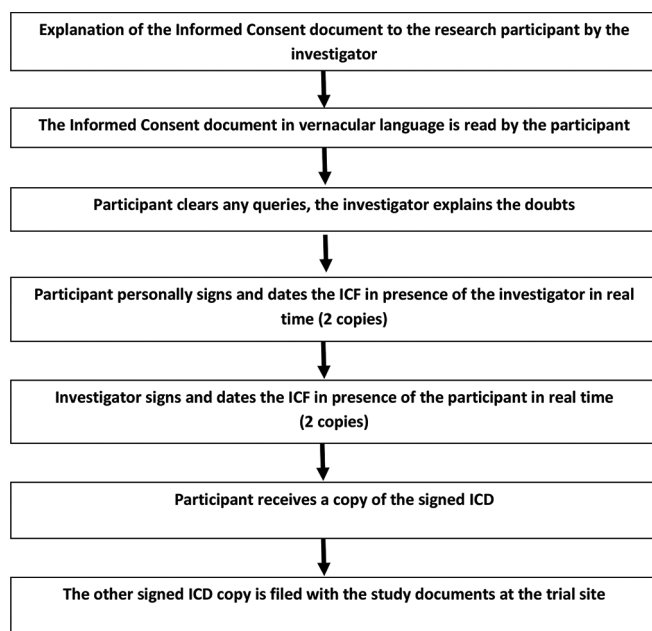


Figure 1: Process of obtaining written informed consent in case of a literate participant^[16].

influenced by the stakeholders of the research and is able to read the SIF, ICF and any other written information supplied to the participant.^[16]

Current Regulation

Audio Visual recording of Informed consent process:

Current regulations in India mandate audiovisual (AV) recording of the informed consent process for all trials w.e.f 21st October 2013. On 31st July 2015, the original notification was modified, making AV recording mandatory only in cases of vulnerable populations and with research on new clinical entities.^[24] Important elements of the AV recording are:

1. Documentation of Photo Identity for participant/LAR/impartial witness
2. Adequate video camera to record facial details of participant/LAR/impartial witness and the investigator/authorized person present during the consent process (Minimum resolution of 1280 × 780 pixels)
3. Logistic requirements (recordable memory of at least 4 GB, power backup for at least 2 h, microphone system, external hard disk, desktop/laptop computer, CD/DVD/flash drives)
4. Disturbance free environment for both audio and video recording
5. Unrelated persons should not be present during the recording process

Audio recording in informed consent process: This is mandated only in case of clinical trials concerning drugs to treat leprosy and HIV infection.

Archiving of ICF and AV recording: AV recording of the informed consent process with all related documents must be preserved safely for at least a period of 5 years after

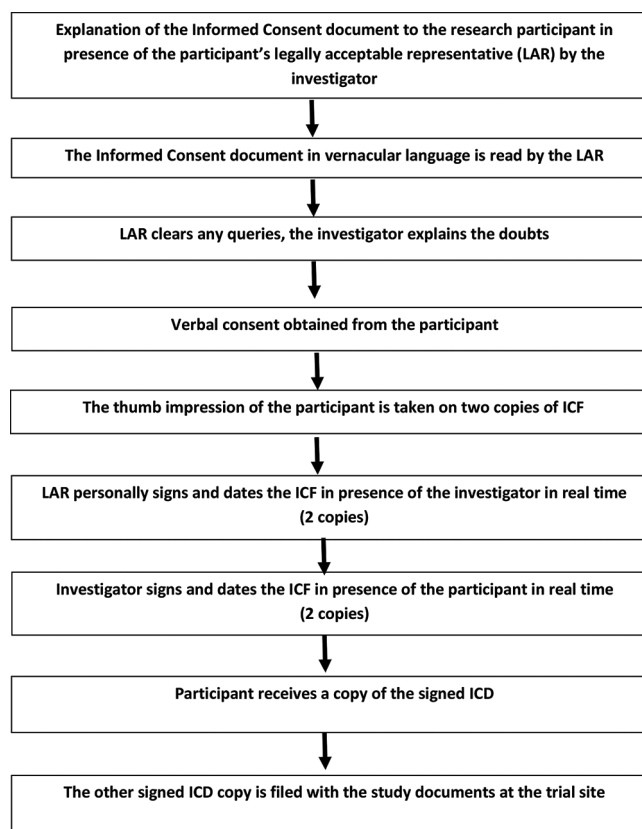


Figure 2: Process of obtaining written informed consent in case of an illiterate participant^[16].

completion/termination of the research, if not permanently. However, the sponsor for a trial/regulatory body may also request for preservation for > 5 years.

Challenges

Medical Emergencies: In such cases, saving life of a person if of prime importance and treatment is permissible for a research participant without his/her consent, in cases of unconsciousness, severe mental illness, grave sickness, and unavailability of another person authorized to give consent. If available, the guardian or LAR can give consent otherwise the consent is taken from the participant after he/she regains the state of understanding the research. Such circumstances must explicitly be stated and addressed in the ICF.

Pregnant Women and Children: Pregnant or nursing women should only be included in a particular research when it intends to study any intervention for their benefit and data on non-pregnant women are not suitable. Risk to the developing fetus/feeding neonate should be minimal and no therapeutic or preventive benefits should be denied. The schedule Y and ICMR guidelines advocate against inclusion of an individual <18 years in a research. Though pediatric patients depend upon their guardian/LAR for providing consent, complete information in simple, common and understandable language has to be provided

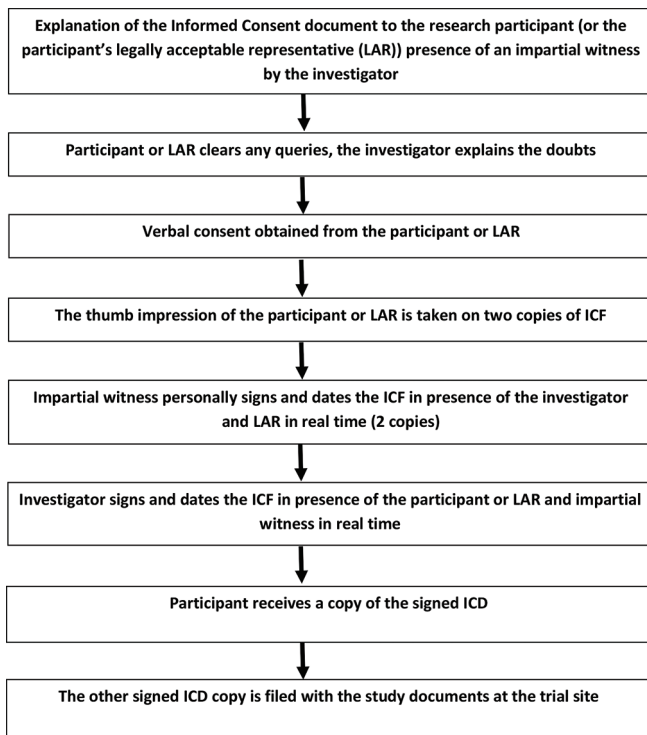


Figure 3: Process of obtaining written informed consent in case of an illiterate participant with illiterate legally acceptable representative^[16]

with due respect to the refusal of the child despite consent from the guardian/LAR. Verbal consent from mature minors (7--18 years) after they read and understand a specially designed assent form, forms the concept of INFORMED ASSENT. Simplicity of the content is crucial in such a case. Therefore, 2 sets of consent forms are required for these mature minors, one being the informed assent form and other the ICF for guardian/LAR.

Vulnerable population: Research participants with reduced autonomy form the vulnerable population, for example, those suffering from terminal illness, undertrial persons, in detention, unemployed/poor socio-economic background, students, homeless/nomads, refugees and racial minority groups. Such population should not be included in a research unless they are specifically benefitted or the research cannot be carried out on other participants. Special ethical consideration is needed for such consent.

Mentally impaired participants: A proxy consent is obtained from the legal guardian or representative.^[16]

Comprehension of the Informed Consent: It has been noted in real-life situations that participants were unaware of their participation in a clinical trial, in spite of their signing the informed consent document. This particularly happens in a society where there exists the atmosphere of “therapeutic misconception” (the trial is being considered as standard medical care)^[1] and ‘paternalism’ (participants doctors to decide on their behalf)^[25] clouds the decision-making capability of the participants. Translation

of informed consent form in vernacular, if not properly done, can lose the essence of the informed consent document and can mislead the trial participants. In a patriarchal society, it is also not uncommon that the male member (father/husband) decides which piece of document the woman would or should sign. In such situation, it would be best to judge the comprehension of the participants regarding the informed consent document by using some existing validated questionnaires.^[25] It needs to be mentioned that ensuring the comprehension is not a regulatory requirement but this exercise would help in strengthening the trust of the participants in the investigator.

Newer approaches with focus on COVID-19 era: The unprecedented wrath of COVID-19 pandemic has posed multiple challenges for biomedical research in terms of social distancing norms, travel restrictions for both the participants and investigators, interruption of logistic and sample transportation and risk of infection for the participant and investigator. Alternative methods for informed consent process during pandemic situation may include:

1. **Electronic consent:** Utilization of technology to create interactive formats, with tools, for example, text, graphics, audio, video, podcasts, interactive web platforms is encouraged to provide research related information and electronic documentation of informed assent/consent for the same.
2. **Digital signatures:** Important for both participant/LAR/ impartial witness as well as the investigator, reviewed and approved by ethics committee *a priori*.
3. **Telemedical documentation:** Can be considered where AV recording is necessary.^[26,27]

Epilogue: Validity and transparency in terms of including all possible information related to the research, risks which are anticipated as well as those beyond anticipation and benefits of enrollment in the research forms an informed consent, which is complete in true sense. The process of informed consent has well traversed the stage of a signed sheet of paper to become a multi-faceted bridge between the researcher and participant to ensure autonomy, justice, beneficence and non-maleficence on the participant’s part and confidence, compliance and ethical research for the physician/researcher.

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Conflicts of interest

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