Indian Council of Medical Research
Govt. of India

INSTRuCT
Indian Stroke Clinical Trial Network

Workshop Report
INSTRuCT Network: Clinical Trial Development and Management

July'2018

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ACRONYMS AND ABBREVIATIONS

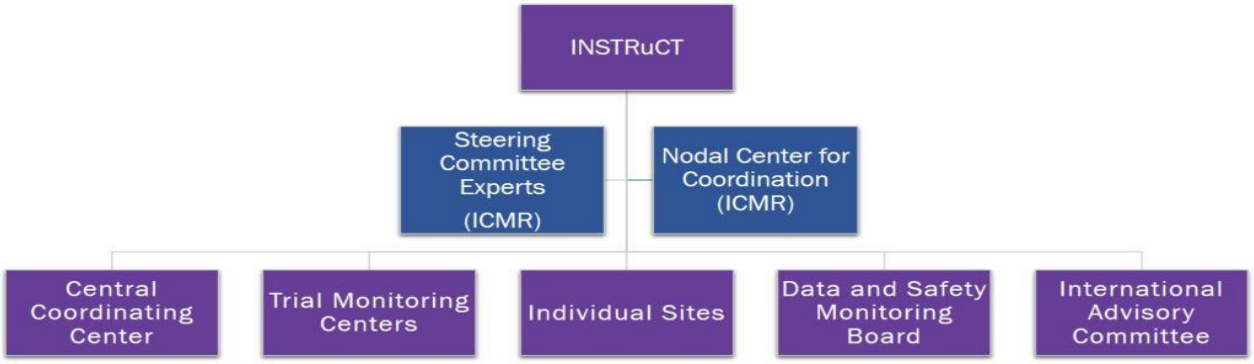
CCC	Clinical Coordinating Center
CT	Clinical Trial
CTRI	Clinical Trial Registry- India
DBT	Department of Biotechnology
DSMB	Data Safety Monitoring Board
EC	Ethical Clearance
ENCHANTED	Enhanced Control of Hypertension and Thrombolysis Stroke study
ERICS	Early Remote Ischemic Conditioning in Stroke
IA	India Alliance
ICMR	Indian Council of Medical Research
INSTRuCT	Indian Stroke Clinical Trial Network
LMIC	Low and Middle Income Country
LOI	Letter of Intent
RCT	Randomized control trial
RESTORE	AyuRvedic TrEatment in the Rehabilitation of Ischemic STrOke Patients in India: A Randomized controllEd trial
SAP	Statistical Analysis Plan
SPRINT India	Secondary Prevention by Structured Semi-Interactive Stroke Prevention Package in INDIA

INTRODUCTION

Stroke incidence in India ranges from 135 to 145 per 100,000, population. ICMR's recent Ludhiana population based Stroke Registry observed that 25% of the patients are below 49 years of age. Though India has good epidemiological data on stroke, the country lags behind in conducting large scale clinical trials and multicenter research in stroke. A vast majority of stroke trials have been carried out in Caucasian population e.g. acute thrombolysis trials, imaging related studies and secondary prevention trials. The findings of these trials may not be applicable to Indian population. In order to answer simple research questions in stroke treatment, genetics and prevention a large sample of patients is required which can be undertaken through a well structured **Stroke Clinical Trial Network** in India. Indian Council of Medical Research (ICMR) has funded Indian Stroke Clinical Trial (***INSTRuCT) Network*** to conduct small and large clinical trials and research studies to advance acute stroke treatment, stroke prevention and recovery and rehabilitation following a stroke. This network of 25 hospitals in different parts of the country is designed to:

- Develop a world-class health infrastructure for carrying out stroke trials in India for serving as a pipeline for new potential treatments for patients with stroke and those at risk of stroke.
- Develop a portfolio of stroke trials in the areas of prevention, acute care, rehabilitation and chronic care.
- Work with professional, industry, academic and funding bodies (within and outside the country) to enhance and increase Indian stroke clinical trials
- Provide an educational platform for stroke physicians to build capacity for undertaking country specific stroke clinical trials

ORGANIZATIONAL STRUCTURE OF INSTRuCT:



- **Central Coordinating Center (CCC):** The stroke unit of Christian Medical College, Ludhiana is the Central Coordinating Center. The CCC creates and monitors online databases of all clinical trials which are done using this network. The CCC is equipped with infrastructure such as Servers (1-standard and 1 back-up), IT personnel and two national coordinators. The IT staff design and maintain the online databases. The clinical research coordinators look after the trial management across all centers.

- **Trial Monitoring Centers (TMC):** Christian Medical College, Ludhiana and SCTIMST, Trivandrum monitor all the trials done under the INSTRuCT. The north Indian centers are monitored by CMC Ludhiana and the south Indian centers by SCTIMST Trivandrum.

- **Data and Safety Monitoring Board (DSMB):** There is an independent DSMB created by ICMR which monitor all the trials in the network.

- **Individual Sites:** All the 27 centers have 1 research coordinator who conduct and oversee all the trials under the INSTRuCT network in that particular center.

- **International Advisory Committee (IAC):** Stroke experts from NIH Stroke-NET, Canadian Stroke Consortium, UK Stroke Network and Australian Stroke Trials Network are part of the IAC. They advise on the key issues of the Network. This helps us to be a part of the Global Alliance of Independent Networks focused on Stroke Trials (GAINS). Prof. Gary Ford, UK, Prof. Broderick, USA, Prof. Demchuk, Canada, Prof. Anderson, Sydney, Prof. Lindley, Sydney and Dr. Billot, Sydney and Dr. Yuko Palesch, NIH-Stroke-Net, USA is in the IAC for the next five years. All the trial protocols sent to the IAC for comments and they join the meetings held by ICMR through video conference. These meetings are held once or twice a year.

OBJECTIVES OF THE WORKSHOP

The objectives of the workshops were:

- To increase the capacity of participating centres in INSTRuCT network for designing and conducting stroke clinical trials
- To explore research priorities for stroke clinical trials India
- To conduct a competition on 'Letter of Intent'

Key resource person for the workshop were:

- Dr. Jeyaraj Pandian, CMC, Ludhiana
- Dr. Kameshwar Prasad, AIIMS, New Delhi
- Dr. Rohit Bhatia AIIMS, New Delhi
- Dr. Prem Pais, St John NAMS, Bengaluru
- Dr. Sylaja P N, SCTIMST, Thiruanathapuram
- Dr. JMK Murthy, CARE, Hyderabad
- Dr. J S Thakur, PGIMER, Chandigarh
- Dr. Pallab Maulick, George Institute of Global Health, Hyderabad
- Dr. Dennis Xavier, St John NAMS, Bangalore
- Dr. L Jayaseelan, CMC Vellore
- Dr. Mahesh Kate, CMC, Ludhiana
- Dr. Habib Hasan, PHFI, New Delhi
- Dr. Sankara Sarma, SCTIMST, Thiruvanathpuram
- Dr. Yogesh Kalkonde, SEARCH, Gadchiroli
- Dr. Suveera Dhup, India Alliance, New Delhi
- Dr. Meenakshi Sharma, ICMR, New Delhi
- Dr. Prakamya Gupta, ICMR, New Delhi

Day 1 (25th July'2018)

Technical Session 1:

Speakers from CMC Ludhiana, AIIMS New Delhi, SCTIMST Thiruanathapuram and St. Johns Research Institute, Bengaluru delivered presentations on effective designing of clinical trials and shared their experiences of INSTRuCT Network.

Introduction To Stroke Clinical Trial Development Workshop

Dr. JD Pandian, CMC, Ludhiana

ICMR has taken a lead in stroke clinical research by developing an infrastructure under the INSTRuCT network. The major goal of creating an Indian Stroke Clinical Trial Network is to conduct simple pharmacological and non-pharmacological stroke clinical trials relevant to our country. The network is conducting two national trials, **Secondary Prevention By Structured Semi-Interactive Stroke Prevention Package in INDIA (SPRINT INDIA)** and **AyuRvedic TrEatment in the Rehabilitation of Ischemic STrOke patients in India: A Randomized ControllEd trial (RESTORE)** and is providing infrastructure support for two international trials, **Enhanced Control of Hypertension and Thrombolysis Stroke study (ENCHANTED) Funded by NHRMC, Australia and Early Remote Ischemic Conditioning in Stroke (ERICS) trial funded India Alliance The Wellcome Trust/DBT. Phase 2a trial**. The INSTRuCT platform provides support to academic international trials of importance to the country thereby hoping to leverage benefits of these trials to the country.

SPRINT INDIA Trial is a multicenter, randomized, parallel-design, adaptive and blinded end-point clinical trial of sub-acute stroke patients. Dr Mahesh Kate will be discussing the details of this trial during this session.

Approximately 50% of patients have persistent motor disability following stroke. Ayurveda has certain beneficial effects in the rehabilitation of stroke patients. Since their efficacy in human stroke subjects is unproven, it is planned to study their safety and efficacy in improving the motor functions of stroke patients in a randomized trial, **RESTORE**.

ENCHANTED is an independent, investigator initiated, international collaborative, quasi-factorial randomized controlled trial involving a package of 2 linked comparative treatment arms. The rtPA dose arm of the study concluded with a publication of the results in May 2016. The BP intensity arm of the study is ongoing. The Trial was initiated in India in September 2017.

Despite best medical management, high-risk transient ischaemic attack (TIA) and acute ischaemic stroke are associated with early neurological deterioration (END), recurrent strokes and death, highest in the first week and persists for 12 weeks. Remote ischaemic conditioning (RIC) involves brief-cyclic ischaemia and reperfusion of a distant organ (upper arm muscles) to protect at-risk (cerebral tissue) organ tissue by increasing ischaemia tolerance. Its role in high-risk ischemic stroke patients remains unknown. The **ERICS** study aims to assess feasibility and safety of early RIC in high-risk ischaemic stroke patients (Phase IIa) and to assess predictors of favourable RIC therapy in high-risk ischaemic stroke patients.

Dr. Pandian then described the **Letter of Intent competition.** Around 34 neurologists with interest in stroke from all over India were invited for workshop. The speakers and experts were asked to contribute to at least 5 stroke research ideas as hypothesis statement. In view of the mandate of INSTRuCT, the ideas needed to be in form of clinical trial and not observational studies. The ideas needed to be drafted as LOI letters to allow one to communicate core ideas to a funding agency. Ten research ideas which were pertinent, contextual, current, and applicable to regional needs or speaking to national requirements were selected out of 100 ideas received. The research ideas received from participants were further formalized with the help of expert/s during the workshop. At the end of workshop, all ten teams will pitch their ideas before the experts and three deliverable ideas will be selected for full proposal development. These proposals will be reviewed by task Force Group of INSTRuCT and funded by ICMR.

Secondary Prevention by Structured Semi-Interactive Stroke Prevention Package in INDIA trial (SPRINT INDIA)

Dr. Mahesh Kate, CMC, Ludhiana

The SPRINT India Trial was started in April 2017. The objective of the SPRINT trial is to assess the role of a structured semi-interactive stroke prevention package to reduce the risk of recurrent strokes, myocardial infarction and deaths in patients with sub-acute stroke after one month. SPRINT India is a multicenteric (25 centers across the country), randomized, parallel-design, adaptive and blinded end-point clinical trial of sub-acute stroke patients. The participants will be block randomized into two groups in a 1:1 ratio; the intervention arm will receive a Structured Semi-Interactive Stroke. A Stroke prevention workbook according to the Federal Plain Language Guidelines and National Culturally and Linguistically Appropriate Services (CLAS) Standards has been developed. Personalized text messages providing reminders for medications, motivation to adopt healthy habits, and health information to improve dietary habits, increase physical activity, encouraging smoking and alcohol intake cessation to be sent via SMS and videos have been developed in nine different languages for the intervention arm patients/caregiver. The patient recruitment was initiated in April'2018. Till date, 975 SMS and 92 video messages were sent

in 4 different languages and a total of 87 patients have been enrolled in the trial. It is estimated that 6000+ patients are planned to be recruited in next 2 years.

How to conduct a review of literature and its benefits?

Dr. Rohit Bhatia, AIIMS, New Delhi

PICOT format is a helpful approach for summarizing research questions for a study protocol.

(P) – Population refers to the sample of subjects one wish to recruit for your study.

(I) – Intervention refers to the treatment that will be provided to subjects enrolled in your study.

(C) – Comparison identifies what you plan on using as a reference group to compare with your treatment intervention. Many study designs refer to this as the control group. If an existing treatment is considered the 'gold standard', then this should be the comparison group.

(O) – Outcome represents what result you plan on measuring to examine the effectiveness of your intervention.

(T) – Time describes the duration for your data collection.

Various libraries and databases e.g. Scopus, Pubmed, Google Scholar and/ or Cochrane are available online for conducting review. Review of literature can be performed by using different 'keywords' and applying filters. Examples of conducting review were given.

Writing a good research protocol

Dr. Prem Pais, St John NAMS, Bengaluru

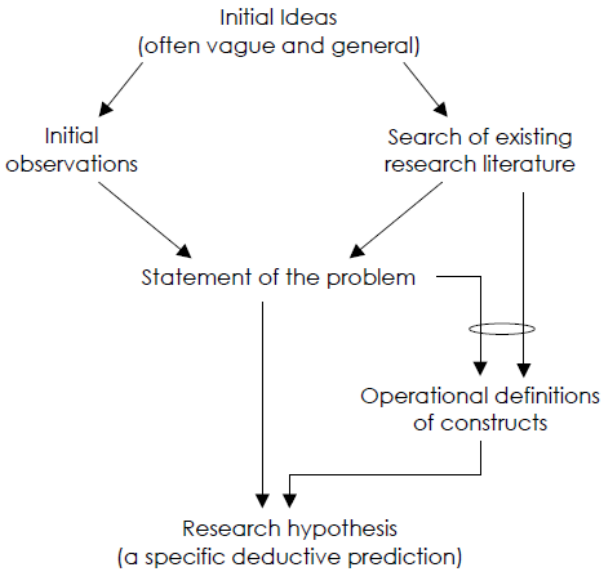
The purpose of clinical research is to increase knowledge about the human condition for the betterment of all especially the disadvantaged section. Clinical research answers important questions which will improve the health of our patients. The components of a research protocol are summary, introduction, research/ study question, background/ rationale, study design, sample size, subject eligibility criteria, safety, regulatory guidance and consent etc. Developing a good research question/ hypothesis is the most important part in a study. Examples of CREATE Trial published in JAMA with its primary and secondary objectives was highlighted. A thumb rule while planning a study is '**FIRE**': **Feasible** (Number of subjects, technical feasibility, affordable in time and money), **Interesting, Relevant** (Scientific Knowledge, Health policy, Clinical practice, Further research) and **Ethical.**

How to write a good hypothesis statement

Dr. PN Sylaja, SCTIMST, Thiruvananthapuram

Hypothesis is an intelligent guess or prediction that gives direction to the researcher to answer the research question. It helps to translate the research problem and objective into a clear explanation or

prediction of the expected results or outcomes of the study. Hypothesis provides clarity to the research problem and research objectives, explains or predicts the expected results or outcome of the research, indicates the type of research design, directs the research study process and identifies the population of the research study that is to be investigated or examined.



She explained that the hypotheses are of two types: research hypothesis and null hypothesis. A research hypothesis tentatively states the existence of relationship between the independent and dependent variables whereas a Null hypothesis (H_0) is used for statistical testing and interpretation of statistical outcomes. It states the existence of no relationship between the independent and dependent variables. The researcher tries to reject or nullify the hypothesis.

The session ended with a round of exercise conducted by Dr. Vishnu.

Technical Session 2:

Technical Session 2 was devoted to learning about the study design, writing a good abstract and letter of intent.

Writing a project summary and abstract

Dr. JMK Murthy, CARE, Hyderabad

A lay abstract is a brief summary of a research project that is used to explain complex ideas and technical and scientific terms to people who do not have prior knowledge about the subject. This is intended to explain why the research is being suggested, what researchers aim to achieve, and how this may impact the quality of life of people with a particular disease. The summary is important to communicate the nature and importance of research to the general public, help adjudicators score grant applications and encourage multidisciplinary work by helping those in unrelated disciplines fully understand each other's research. The language of the summary should preferably be neutral and should make an assumption of the grade, vocabulary and experience of the targeted audience. The statistical information provided needs to be simple and contextual. However, the summary should not compromise science. The scientific article abstract should reflect the core observations of the study and whether the observations provide answers to the study questions. The contents of abstract should reflect the title of the study and the essentials of what has been reviewed. The scientific article abstracts are of two types- structured and un-structured. A structured abstract includes a brief **Introduction/Background, Material and Methods (**Setting, participants, study design, size, duration of the study, outcomes and approval by the Institutional Ethics Committee) **Statistical Analysis, Results, and Conclusions/Interpretation.**

How to write a Letter of Intent?

Dr. J S Thakur, PGIMER, Chandigarh

A Letter of Intent (LOI) is a short, 1–3 page letters that allows one to communicate core ideas to a funding agency. LOI contains vital material for both the applying organization and the funding source. LOI's are used to provide the funding source with information and insights, which help grantors determine which organizations are most appropriate to apply for their grant. The goal of an LOI is to get invited to submit a full grant proposal. A good LOI can save both applicant and funding agency time and effort. The various components which need to be included in a LOI are summary statement, why & how the project will be done and outcome and tentative budget of the project.

There are a variety of sources for funding including the government, pharmaceutical companies and research organizations which can be targeted for obtaining grants. The mandate of these agencies needs to carefully examine while applying for funds.

Study Design

Dr. Pallab Maulick, George Institute of Global Health, Hyderabad

A bias is any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease. There are two types of bias: selection bias and information bias (e.g. recall bias, reporting bias and surveillance bias). Various issues related to study design are selection bias, confounder/s, mediator and effect modifier interaction. With the help of several examples, various study design such as cross sectional studies, cohort studies, case series, randomized controlled trials (RCTs), etc were explained. The RCTs remain the gold standard for assessing intervention efficacy. The important features of RCTs are clinical equipoise, uncertainty principle, randomization, allocation concealment, blinding, compliance, intention-to-treat (ITT) or "per protocol" analysis. There are two types of RCTs: (i) Cluster randomized RCTs in which individuals are randomized in groups (e.g. hospitals, villages and schools) and intervention applies to a specific group; (ii) Factorial RCTs in which more than one intervention is tested at once. Well-conducted RCTs provide best evidence for effectiveness of a treatment/program. Also, different study designs may be used depending on condition, nature of intervention and cost.

The participants enthusiastically participated in round of exercise conducted by Dr. Vishnu.

Technical Session 3 & 4:

Technical Session 3 & 4 focused on the discussions on the randomized control trials for clinical trials, how to perform Sample Size Calculation and perform Interim analysis and Futility Analysis.

Randomization, stratification and minimization of clinical trials

Dr. Dennis Xavier, St Johns, Bengaluru

The randomization is a process of assigning patients to treatment using a random process. The observational studies tend to have selection bias, henceforth RCTs are the 'gold standard' to evaluate treatments outcome. The treatments administered should be selected by a random process; this process eliminates selection bias, protects from known and unknown confounders and helps achieve a balance of prognosis between the treatment groups and validity for statistical assumptions. Using random number tables or a computer generated number, patients can be randomly assigned to different treatment modality. The treatment administered can also be selected by a random process. The various methods of randomization include simple randomisation, stratified randomisation, paired randomisation, pair wise randomisation and minimisation. Sealed envelopes, automated telephone –IVRS and/ or web-IWRS based randomization can be used for randomization. The process of randomisation is superior as compared to

any other method as it is unpredictable and cannot manipulate, also results in balanced groups and with all known and unknown variables. Examples of randomization used in CREATE Trial published in JAMA, 2005 were highlighted.

Stopping Rules, Interim and Futility Analysis

Dr. Mahesh Kate, CMC, Ludhiana

Interim analysis is the statistical strategy to assess outcome at an earlier time-point before completion of trial enrollment without compromising validity and integrity. In most clinical trials, it is not necessary to perform a statistical analysis after each patient is accrued. In fact, for most multi-center clinical trials, interim statistical analysis are conducted only once or twice per year. Usually this frequency of interim analysis detects treatment effects nearly as early as continuous monitoring. Trial/ Studies can be stopped due to:

i. Treatments convincingly different
ii. Treatments convincingly not different
iii. Side effects or toxicities are severe
iv. Data quality is poor
v. Slow recruitment
vi. Definitive information available from an outside source
vii. Scientific question is no longer important
viii. Adherence to treatment is unacceptably low
ix. Resources to perform study are lost or diminished
x. Study integrity undermined

Various interim analysis methods are Likelihood Method, Bayesian Methods, frequentis method: O'Brien Fleming, Pocock and Haybittle Peto.

O'Brien and Fleming approach: this is a popular method which uses a very small amount of the alpha in the initial stages and reserves a large part of the alpha for the final analyses. For example, when one interim and one final analysis are planned, 0.0054 of the alpha is expended first and 0.0492 reserved for the final analysis. This method ensures that it is difficult to reject the null hypothesis in the early stages of the study, but relatively easy later on.

Pocock approach: this method divides the alpha error equally amongst the total number of analyses planned. For example, if there is one interim and one final analysis, the *p* value expended at each analysis is the same.

Haybittle Peto or Peto approach: this approach uses a miniscule amount of the alpha in the initial "looks" (much lower than the O'Brien and Fleming approach), but the final analysis is always performed using the entire 5% alpha. This method thus makes it easy for the investigators and readers to apply as 5% at the end of the study is what they are comfortable with. The criticism of this approach is that the extremely low alpha values are going to make it almost impossible to stop the study at the early stages.

How to decide outcome variable?

Dr. Rohit Bhatia AIIMS, New Delhi

Outcomes (also called events or endpoints) are variables monitored during a study. These document the impact that a given intervention or exposure has on the health of a given population. Typical examples of outcomes are cure, clinical worsening, and mortality. It is important to decide on the study outcomes "*a priori"* based on the focused research question and hypothesis and the sample size calculation shall follow methodically based on the outcome in question. It is critically important to define outcomes as it helps decide a focused end point and avoids cherry picking for analysis. Typically, two forms of outcomes are planned: *Primary* and *Secondary*. The primary outcome is the key endpoint and is the most relevant variable that answers the the main research question; this should ideally be *patient centric*. Secondary outcomes are additional outcomes monitored to help interpret the results of the primary outcome efficacy and safety and could provide preliminary data for a larger study. You should NOT BE TEMPTED to monitor SEVERAL outcomes as the effort and cost to monitor various outcomes may not be cost effective and relevant. Other forms of outcome analysis could be to use surrogate outcomes like biomarkers or composite outcomes like death, dependancy, stroke, MI in a vascular endpoint study. These help increase the power of the study when events are rare and competitive, but has problems and sometimes underestimate the results of the study which may be important. It is also important to

understand reasons of failure of primary outcomes by reasoning including some of the following points: *was the primary outcome clearly defined?, was the study powered enough?, was the study design ok?, was the correct population selected?, how methodically was the trial conducted etc.*

Statistical Analysis Plan (SAP) for Clinical trial

Dr. Sankara Sarma, SCTIMST, Thiruvanathpuram

The proposals have brief listing of Statistical aspects of the trial in the Statistics Section and are usually restricted to sample size justification, sample selection, randomization procedures and statistical methods planned. However, other aspects that influence the choice of statistical methods which should also be enlisted in a proposal/protocol are (i) Definition of the study populations with inclusion/exclusion rules (ii) Definition of variables including the outcomes (iii) Measurement methods (iv) Details on objectives, study design and hypotheses (non-inferiority/superiority trial). The SAP should be presented as a document listing the details of not only the statistical methods that will be used, but all relevant details that have bearing on the data analysis, interpretation and reporting. The policies related to stopping rules are interim analysis planned, how often or when they should be done and what to look for in the interim analysis. The sample size justification, sample selection and Randomization procedures and statistical methods planned for analysis. The SAP should provide details on the planned methods in every aspect that can influence the findings and conclusions of the trial. The SAP is an essential standalone document that gives details on the planned statistical analysis and other essential information to do the data analysis and interpretation properly.

Sample Size Calculation: Randomized Controlled Trial

Dr. L Jayaseelan, CMC, Vellore

Hypothesis testing is to test whether evidence for assumptions or statements we make about our research objective (alternative hypothesis) against the previous or existing history of that particular research objective (null Hypothesis). There are two kinds of errors, which by design cannot be avoided (i) Type I errors happen when we reject a true null hypothesis (ii) Type II errors happen when we fail to reject a false null hypothesis. The value of alpha, which is related to the level of significance has a direct bearing on type I errors. Alpha is the maximum probability that can have a type I error. For a 95% confidence level, the value of alpha is 0.05. This means that there is a 5% probability that will reject a true null hypothesis. Type II errors are equivalent to false negatives e.g. A type II error would occur if we accepted that the drug had no effect on a disease, but in reality it did. The probability of a type II error is given by the Greek letter beta. The power of study is defined as the probability that if a true difference of stated

magnitude existed then the study would have picked it up as statistically significant. The power of the study is complement of Beta error.

Researcher's Decision	Reality: Null True (No Difference)	Reality: Null False (Difference)
Null. True (No Difference)	Correct	Type II error (or) Beta error
Null. False (Difference)	Type I error (or) Alpha error	Correct Power = (1-beta)

Technical Session 5:

How to write an effective budget

Dr. Meenakshi Sharma, ICMR, New Delhi

Once a proposal is submitted by a PI, ICMR assigns the proposal for Peer reviewers. The peer reviewers review the project & score based on Relevance, Novelty, Methodology, Track Record and Institutional facilities etc. The scored applications are sent to Project Review Committee (PRC) and based on the comments of the reviewers or PRC members, the proposals are finally recommended or rejected. The PRC recommendations are finally approved by the DG, ICMR. In the INSTRuCT Trial Development Process involved initial discussion on the concept note with INSTRuCT Investigator and Coordinators. The investigator then submitted the concept note with preliminary budget to INSTRuCT coordinators. The concept note was then sent to ICMR for review by Task Force Experts. Once the concept note was approved, the investigators developed full proposal and final budget. The full Proposal along with Budget, IEC Review, CTRI registration, DCGI clearance etc are submitted to ICMR for review. The ICMR task force experts review the full proposal & budget. The proposal was finally approved by task force committee and then by DG, ICMR. The Clinical Trials budgets are prepared according to (i) Overall Budget (ii) Per Year Budget under the major budget heads (Staff, Recurring, Non recurring, contingencies, overhead charges, Travel and insurance) and mentioning the year wise budget and overall budget. The principle guiding budgeting should reflect the scope of work (i) Overall Budget: Total Budget of the entire Study (ii) Coordinating Centre Budget: to a PI in a multicenteric study responsible for all sites (iii) Per Site Budget: to local site PI for starting trial, per patient enrollment, and study

close-out. In INSTRuCT, the infrastructure budget has been provided for 27 sites including two Coordinating Centres (One in North and One in South - CMC, Ludhiana and SCTIMST, Thiruvanathpuram). ICMR Stroke Clinical Trials are Milestone Based and the study will be stopped if recruitments are not as per timelines.

Dissemination Policy for stroke trials

Dr. JD Pandian, CMC, Ludhiana

The project dissemination helps in promoting awareness among the medical community, policy makers and public. A dissemination meeting should involve all investigators, government officials and funding agencies. This helps to discuss the public health impact of the trial and propose recommendations for policy formulation. The ATTEND Trial: Dissemination Meeting was held in Nov'2017. The objective of the ATTEND trial dissemination were (a) To discuss the public health impact of the trial and stroke rehabilitation in India (b) To share ATTEND trial results (c) To propose recommendations at the policy level for systemic support for stroke rehabilitation.

Building health economics studies in clinical trial

Dr. Habib Hasan, PHFI, New Delhi

It is important to examine the relationship between the outcomes of a clinical trial and the costs of the medical therapy under study. The economic evaluation in clinical trials provides practical advice on how to conduct cost-effective analyses in controlled trials of medical therapies. The economic evaluation measures the value of alternative course of action or the opportunity cost. The assessment of 'value' makes explicit importance of viewpoints- an alternative that seems unattractive from one point of view may seem more attractive from another (i.e. cost to one is benefit to another). There are 4 types of economics evaluation i.e. cost minimisation, cost effectiveness, cost utility and cost benefit evaluation. The three important features of economic evaluation are (i) costs and consequences to determine the efficiency (ii) technical efficiency for comparison and (iii) assist in decision making.

In the evening (5:30pm to 7:30 pm) all the teams refined the letter of intent with help of the workshop mentors. It was fun to see all delegates participate till late evening upto 8 pm. The mentors for the session were Dr. J D Pandian, Dr Jayasheelan, Dr. PN Sylaja, Dr. Meenakshi Sharma, Dr. JMK Murthy and Dr. Prem Pais.

Day 2 (26th July 2018)

Technical Session 1:

The next day first session started with an outline of the key messages for conducting clinical research in India.

Research in Resource Poor Setting- Gadchiroli

Dr. Yogesh Kalkonde, SEARCH, Gadchiroli

Conducting research in resource poor setting might be a big hurdle but high quality research can be done in this environment using specialized approach of verbal autopsy. Gadchiroli is one of the most underdeveloped districts of India. It has a population of about 10 Lakhs of which 89% are rural and around 40% are tribal population. The Physician: population ratio is around 1:5000 as compared to 1:1300 in India. Only one neurologist is available in the district. Due to lack of brain imaging, the stroke types cannot be identified. Also, there is high probability of missing minor strokes cases. In resource constraint setting, the adequate sample size is needed to estimate the true mortality rate of stroke with a precision of ±5% at 95% confidence and considering a design effect of 1.5. A three stage approach may be adopted to get high quality data (i) Door-to-door survey using a well validated screening questionnaire (ii) Evaluation by a trained physician (iii) patients whose diagnosis of stroke was uncertain were evaluated by a neurologist. However, the data from one rural setting (Gadchiroli) cannot be representing all rural India.

Key issues in Randomized Clinical Trials

Dr. Kameshwar Prasad, AIIMS New Delhi

The different study design RCTs include: Parallel group vs. cross-over, Efficacy (explanatory) vs. effectiveness (pragmatic), Cluster randomized vs individual randomized, Factorial design and/or single centre vs multi-centric study. The random allocation should be done either by sequence generation or concealment of allocation. Randomization can be done by similarly packed drugs and placebo in random sequence, sequence generation using sealed envelopes, automated telephone and/ or computer based. In the Laparoscopic appendectomy trial, to avoid ambiguity while using envelopes method for randomisation, the envelopes should be sealed opaque, sequentially numbered. To promote smooth running of the trials both the groups should be treated equally, new treatment group should not receive extra care or intervention (co-intervention), avoid mixing of patients within the groups and patients should comply with the allocated intervention. For interventional studies, the intervention should be blinded, specified and standardized for all. The analysis of interventional studies could be classified: (A) Based on how events are counted such as (i) Intention to treat (ii) Per-protocol (iii) as treated (iv)

sensitivity analysis (B) Based on which outcomes are analyzed (i) primary (ii) secondary (iii) adverse effects and (C) Based on patient subgroups/recruitment (i) Subgroup analysis or (ii) Interim analysis.

ICMR Funding Mechanism

Dr. Prakamya Gupta, ICMR-Hqrs, New Delhi

ICMR is the apex body in India for the formulation, coordination and promotion of biomedical research, is one of the oldest medical research bodies in the world. ICMR's mandate is to undertake and support basic, epidemiological, applied and operational research in the areas of national public health importance using tools including those of modern biology. ICMR provides financial assistance to promote research work in the fields of medicine, public health and allied areas under its Extramural Research Programme. Various Extramural Research and supported by ICMR include Adhoc Projects, Task force projects, Cohort Study/ National Registry, Center for Advance Research and Excellence. Apart from the research projects, ICMR also supports Studentships (Short Term Studentship, Junior Research Fellowship, SRF/ RA Fellowship, Post Doctoral Fellowship), Clinical Research (Clinical Scientist Scheme, MD/MS/PhD Programme, MD/MS/ MCh thesis support) and Travel grants. The ICMR thrust areas are: Communicable diseases, non communicable diseases, reproductive and child health, nutrition, basic sciences, medicinal plants and traditional medicine, Ethics, IPR and socio behaviour sciences. Any project submitted in these domain areas are evaluated by external experts review committee. The applications submitted to the ICMR are evaluated for scientific and technical merit, novelty, national importance, ICMR priority research area, methodology, ethical issues, budget of the proposal and PI Track record. The proposal was finally approved by committee chairperson and then by DG, ICMR. The approved projects are monitored from time to time in the form of interim or annual report. The expert committee may suggest modification in the protocol or may terminate the project if the progress is not upto the mark.

Developing Collaborations Lesson from Indo-US Registry

Dr. Sylaja P N, SCTIMST, Thiruvananthapuram

The goal of Indo-US research collaboration aims to develop infrastructure for research tool and data sharing. The project compares stroke risk factors, stroke subtypes and outcomes of stroke in India and US. The Indo-US Bilateral Stroke Research collaboration aims to lay the foundation for Indo-US research collaboration, Infrastructure for research tool and data sharing, comparison of stroke risk factors, stroke subtypes and outcomes of India and US. The collaborative work will help in improvement of infrastructure and training the research coordinators, improvement in the quality of care in the stroke unit, data collection and data sharing and higher impact factor publication. The data from the Indo-US registry will also aid in designing future genetic and imaging studies.

India Alliance "The Game Changer"

Dr. Suveera Dhup, India Alliance, New Delhi

The India Alliance (IA) is visionary partnership between Wellcome Trust and Department of Biotechnology (DBT). The £160 million initiative aims to (i) empower researchers to do internationally competitive research (ii) facilitate engagement of the scientific community with society (iii) encourage diversity, inclusivity, and transparency in science and (iv) enhance India's research ecosystem. The mandate of IA is to Support biomedical research that is relevant to human and animal welfare, build scientific capacity in India and build excellence in biomedical science community in India. The IA promotes fellowships, workshops, public engagement and support for relevant scientific events at research institutions in India. The IA provide fellowship grant to Early career, Intermediate, Senior and Magdarshi fellowship for basic research or clinical & public health research.

The IA has independent online grants management system (IASys) for transparent and efficient application and decision-making process. IA provides support at all levels: pre- and post-application and post-funding. The clear and current policy promotes equality, diversity, open access, avoid conflict of interest and plagiarism. The grant application submitted to IA must include motivation, research question, research plan, willingness to move out of comfort zones, demonstration of ownership of ideas, availability of expertise/ mentorship, demonstration of productivity in form of -publications, patents, presentations, mentoring and recommendations and collaborations.

From 2009 to 2018, IA has received ~3000 applications of which only 320 were recommended for awards (with success rate of only 11.2%) from 93 institution in 34 cities. The domain distribution of these awards comprised 78.43% awards for basic research and 21.56% awards for clinical and public health research. Around 32.18% of the total recommended awardees are from overseas.

Annexure-I

PROGRAM SCHEDULE

Day 1

	Timings	Speaker
Registration	8 am-8: 20 am	
Introduction of the Programme and LOI Competition	8:20 am –8:30 am	Jeyaraj Pandian, CMC, Ludhiana
Need of Clinical Trial Research Training Workshop	8: 30am –8:40am	Dr Meenakshi Sharma, ICMR Hqrs, New Delhi
How to conduct review of Literature	8: 40am –9:00 am	Rohit Bhatia AIIMS, New Delhi
Good Protocol Writing Practices	9:00 am- 9:20 am	Prem Pais, St John NAMS, Bangalore
How to frame a good Hypothesis Statement	9:20 am- 9:40 am	Sylaja P N, SCTIMST, Thiruanathapuram
Get up and Exercise Regroup and Synthesize the LOI	9:40 am – 10:10 am	
Writing a Good Lay Person Summary and Abstract	10:10 -10:30 am	JMK Murthy, CARE, Hyderabad
How to write a Letter of Intent	10:30 - 10:50 am	J S Thakur, PGIMER, Chandigarh
How to choose a Study Design	10:50 - 11:10 am	Pallab Maulick, George Institute of Global Health, Hyderabad
Get up and Exercise Regroup and Synthesize the LOI	11:10 am-11: 40 am	
Randomization, Stratification and Minimisation: What is what	11:40 - 12:00 pm	Dennis Xavier, St John NAMS, Bangalore
How to write about Study Procedures/ Intervention in clinical trial protocol	12:00-12: 20pm	Dheeraj Khurana, PGIMER, Chandigarh

How to decide outcome variable	12:20 -12:40 pm	Rohit Bhatia AIIMS, New Delhi
Eat some treats Is the LOI ready to compete		12:40 pm- 1:40 pm
Effect size and Sample Size Calculation	1:40 pm- 2:00pm	L Jayaseelan CMC Vellore
Statistical Analysis Plan for Clinical trial	2:00 pm- 2:20pm	Sankara Sarma SCTIMST, Thiruvanathpuram
Interim analysis and Futility Analysis	2:20 pm- 2:40pm	Mahesh Kate, CMC, Ludhiana
Get up and Exercise ***Regroup and Synthesize the LOI***		2:40 pm- 3:10pm
Write effective Budget	3:10pm- 3:30 pm	Meenakshi Sharma ICMR, New Delhi
How to build in Health Economics studies in clinical trial	3:30 pm- 3:50 pm	Habib Hasan, PHFI, New Delhi
Dissemination Policy	3:50 pm- 4:10 pm	Jeyaraj Pandian CMC, Ludhiana
Get up and Exercise ***Regroup and Synthesize the LOI***		4:10 pm-4: 30 pm
Break out in pre-defined groups of 4-5 (may vary depending on number of participants) to develop LOI	4:30 pm – 6:30 pm	
Discuss Preliminary drafts with the Experts assigned	6:30 pm-7: 30 pm	
Eat some treats ***Is the LOI ready to compete***		7:30pm – 8:30pm
Revise draft over the evening and over the night		

Day 2

Clinical Research in India		
Research in Resource Poor Setting	8:00 am-8: 20 am	Yogesh Kalkonde, SEARCH, Gadchiroli
Low Cost Solutions	8:20 am- 8:40 am	Kameshwar Prasad
Clinical trial work flow in India	8:40 am- 9:00 am	Jeyaraj Pandian CMC, Ludhiana
Developing Collaborations Lesson from Indo-US registry	9:00 am- 9:20 am	Sylaja P N, SCTIMST, Thiruanathapuram
Get up and Exercise ***Submit the LOI Revised*** 9:20 am – 9:50 am		
Funding Mechanism in India		
Indian Council of Medical Research	9:50 am – 10:10 am	Meenakshi Sharma ICMR, New Delhi
Department of Biotechnology, India	10:10 am -10:30 am	Garima Gupta DBT, India
India Alliance "the game changer"	10:30 am- 10:50 am	Suveera Dhup, India Alliance, New Delhi
International Funding	10:50 am- 11:10 am	Vivekananda Jha, George Institute of Global Health, Hyderabad
Exercise with your allies 11:10 am- 11:30 am		
Out of the Box		
Translational Research in India	11:30 am- 11:50 am	Chandrashekhar ICMR, New Delhi
Devices in Stroke	11: 50 am – 12:10 pm	Medtronic

Polypill concept for India	12:10 pm – 12:20 pm	Jayanta Roy AMRI, Kolkata
Results of LOI competition	12:20 pm – 12:40 pm	Judges Panel
Bites with knights	12:40 pm- 1:30 pm	

Annexure-II

Delegates who participated in Workshop

- Dr. Abhishek Pathak, IMS, BHU, Varanasi
- Dr. Anand Vaishnav, VINS Vadodara
- Dr. Arvind Sharma, Zydus Hospital, Ahmedabad
- Dr. Ashish Sharma, RPMC Tanda, HP
- Dr. Biman Kanti Roy, BIN Kolkata
- Dr. Chaitanya Koduri, GGH hospital, Guntur
- Dr. Deepti Arora, CMC Ludhiana
- Dr. Dennis Xavier, St John NAMS, Bangalore
- Dr. Dhananjay Duberkar, Nashik
- Dr. Girish B Kulkarni, NIMHANS, Bengaluru
- Dr. Gunjan Kumar, AIIMS Patna
- Dr. Habib Hasan, PHFI, New Delhi
- Dr. Himani Khattar, CMC Ludhiana
- Dr. Inder Puri, SNMC, Jodhpur
- Dr. J S Thakur, PGIMER, Chandigarh
- Dr. Jeyaraj Pandian, CMC, Ludhiana
- Dr. Kameshwar Prasad, AIIMS, New Delhi
- Dr. KJ Harsha, Bengaluru
- Dr. L Jayaseelan CMC Vellore
- Dr. Madhusudhan BK, BGS Hospital, Bengaluru
- Dr. Mahesh Kate, CMC, Ludhiana
- Dr. Mohd. Sadiq, CMC, Vellore
- Dr. Neetu Ramrakhiani, Fortis Hospital, Jaipur
- Dr. Nirendra Kumar Rai, AIIMS Bhopal
- Dr. P Vijaya, Lalitha Hospital, Guntur
- Dr. Pallab Maulick, George Institute of Global Health, Hyderabad
- Dr. Parag Aradhey, Raipur,
- Dr. Parul Dubey, Goa
- Dr. Pawan Kr Ojha, Sir JJ Hospital, Mumbai
- Dr. Prem Pais, St John NAMS, Bengaluru
- Dr. Rajsrinivas Parthasarthy, Gurgaon

- Dr. Rohit Bhatia AIIMS, New Delhi
- Dr. S Jabeen, NIMS Hyderabad
- Dr. Sanjeev Kumar Bhoi, AIIMS Bhubaneshwar
- Dr. Sankara Sarma, SCTIMST, Thiruanathapuram
- Dr. Shweta Jain Verma, CMC Ludhiana
- Dr. Soaham Desai, Anand, Gujrat
- Dr. Sudheer Ambekar, Jaslok Hospital & Research Center
- Dr. Sudhir Sharma, IGMC Shimla
- Dr. Sulena, GGSMC&H, Faridkot
- Dr. Sunil Narayan, JIPMER, Punducherry
- Dr. Suraj Singh, Imphal
- Dr. Suveera Dhup, India Alliance, New Delhi
- Dr. Sylaja P N, SCTIMST, Thiruanathapuram
- Dr. Thomas Mathew, St John, Bengaluru
- Dr. Vishnu Ranjith, SCTIMST Trivandrum
- Dr. Vishnu VY, AIIMS, New Delhi
- Dr. Vivek Nambiar, AIIMS, Kochi
- Dr. Y Muralidhar Reddy, Care Hospital, Hyderabad
- Dr. Yashpal Singh, Himalayan Hospital, Dehradun
- Dr. Yogesh Kalkonde, SEARCH, Gadchiroli
- Dr.JMK Murthy, CARE, Hyderabad
- Mr. Rachit Jhaveri, BETiC, IIT Mumbai
- Mr. Rahul Huilgol, CMC Ludhiana
- Mr. S Balasubramaniam, Medtronic, Chennai
- Ms Mona Galhotra, Medtronics

ICMR

- Dr. Chandershekhar, Division on ITR, ICMR
- Dr. RS Dhaliwal, Division of NCD, ICMR
- Dr. Meenakshi Sharma, Division of NCD, ICMR
- Dr. Ravinder Singh, Division of NCD, ICMR
- Dr. Prakamya Gupta, Division on ITR, ICMR
- Ms Shilpi Kumari, Division on ITR, ICMR

- Mrs Anju Kumar, Division of NCD, ICMR
- Mr Anil Lakhera, Division of NCD, ICMR
- Mr. Nabendu Gupta, Division of NCD, ICMR
- Ms Payal Kumari, Division on ITR, ICMR
- Ms. Ragini Sharma, Division on ITR, ICMR

The Letter of Intent competition:

Ten research ideas which were pertinent, contextual, current, and applicable to regional needs or speaking to national requirements were selected out of 100 ideas received. The research ideas received from participants were further formalized with the help of expert/s during the workshop. At the end of workshop, all ten teams pitched their ideas before the experts and three deliverable ideas were selected for full proposal development. The three selected best LOI were:

1) Effect of Transcranial Direct Current Stimulation on Early Motor Recovery in Acute Stroke by Dr John Solomon M, Dr Sulena, Dr. Ashish Sharma and Dr Soaham Desai

2) Interventional (Endovascular) by Dr. Vivek Nambiar, Dr. Ashwin Patil, Dr Rajsrinivas Parthasarthy and Dr K J Harsha

3) Safety and efficacy of smart phone based telestroke model for acute stroke treatment by Dr. Sudhir Sharma, Dr Biman Kanti Roy, Dr Inder Puri and Dr Nirendra Kumar Rai.

LOI 1:

Title (< 50 Words)	**Effect of Transcranial Direct Current Stimulation on Early Motor Recovery in Acute Stroke**
Background/ Rationale (<150 words)	Stroke is the leading cause of disability with large number of survivors being functional dependent for some or the other activity of daily living. A very small number of individuals (5 to 20%) regain entire upper limb function post stroke. Transcranial direct current stimulation (tDCS) is a non-invasive, portable, easy to use and relatively inexpensive equipment to modulate cortical excitability. Neuromodulation by tDCS enhances synaptic plasticity.There is evidence supporting the use of tDCS for upper limb recovery in people with sub-acute and chronic stroke but not in the acute stage. In India organized stroke rehabilitation is dismal and there is a need to maximize chances of early recovery in the acute stage. Use of tDCS in the acute period post stroke could improve brain plasticity and result in better motor recovery.
Hypothesis (< 50 words)	Null hypothesis: There will be no difference in the motor recovery between sham and bilateraltDCS groups Research hypothesis: Bilateral tDCSstimulation group will have better motor recovery than sham stimulation
Study Design (<50 words)	Prospective multicenter randomized double blinded sham controlled trial
Screening/ Inclusion/Exclusion criteria (<200 words)	**Inclusion criteria:** Participant will be included in the study if they have: o MCA infarct confirmed radiologically (CT scan) with hemiplegia/paresis o First stroke o Within one week of stroke onset o Age between 18 to 75 years o SAFE score 2-6 **Exclusion criteria:** Participants will be excluded if they are/have: o NIH stroke severity scale score > 20 o Malignant infarction o Patients with cognitive and perceptual deficits interfering in the participation of the study o Clinically significant premorbid levels of disability (mRS>2)

	○ Considerations for surgery ○ Current treatment with drugs that alter CNS activity (Antidepressants and/or Antiepileptic's) ○ Known history of seizures ○ Metallic implants (Cranial, cochlear, cardiac or other)
Study Procedures (<200 words)	Participants will be randomly divided using variable block concealed allocation into one of the 2 groups (bilateral tDCS or sham) which will be centralized. The tDCS will be delivered through stimulator (1X1 Soterix medical systems). The participant will be comfortably seated. Using the 10/20 international EEG system, the electrodes will be placed over the corresponding motor cortex (C3 for left hemispheric stroke and C4 for right hemispheric stroke). Thirty minutes of stimulation with 2mA intensity will be provided in the bilateral tDCS group. Same montage will be employed for sham stimulation group and current will be applied for 30 seconds in the beginning and end of the stimulation with no current in between. All the participants will be screened for the local adverse effects before commencing and after completing each tDCS session. Upper limb training will be started 10 minutes after initiatingtDCSstimulation for another 45 minutes.All participants will undergo regular standard rehabilitation program by therapists not involved in the study. All outcomes will be measured at baseline, On the day of 10thpost tDCSand at post 1 month follow-up by a blinded rater.
Outcome Measures (<100 words)	Primary: ○ Fugl-Meyer upper limb motor subscale Secondary: ○ mRS ○ Modified Barthel index ○ NIHSS score
Sample Size Calculation (<100 words)	Sample size estimation was done using the comparison of means formula and using Fugl Meyer UE subscale as the primary outcome measure. With level of significance at 5% and power at 90% the minimum required sample size was estimated as 25 per group. Considering a dropout of 30%, the adjusted sample size is a total of 90 with 45 participants in each group $n = \frac{2 (Z_{1-\alpha/2} + Z_{1-\beta})^2 X \sigma 2}{d2}$

	$Z_{1-\alpha/2}$ = 1.96 at 5% level of significance $Z_{1-\beta}$ = 1.282 at 90% power Standard deviation = 5 MCID = 4 We will involve 5 center with each centers recruiting atleast 18 participants
Statistical Analysis Plan (<100 words)	Descriptive statistics will be used to analyze the demographic characteristics. The data will be represented with mean and standard deviation. To identify the effect, a repeated measures mixed model ANOVA will be carried out for the primary and secondary outcome measures. The mixed model will analyze both between group and within group changes for the 2 group (bilateral tDCS and sham) at 3 levels of time (pre, post and follow-up).

LOI 2:
TITLE: **DIAVITA** (**DI**rect **A**rterial thrombectomy **V**s br**I**dging **T**hrombolysis in stroke with large **A**rtery occlusion).

Background:

With the approval of recombinant tissue-type plasminogen activator (rtPA) for acute stroke in 1996, for nearly two decades, tPA enjoyed the status of only proven medical therapy for acute stroke. Many mechanical devices were trialled for large vessel clot dissolution/retrieval, but all in vain until 2015, when five trials (MR-CLEAN, ESCAPE, REVASCAT, SWIFT PRIME and EXTEND IA) proved stentrievers as effective additional treatment modality (i.e., in addition to IV tPA) for acute stroke within 4.5 hours. Several observational studies and HERMES meta-analysis raised a question whether IV thrombolysis has any added benefit to mechanical thrombectomy, to which the answer is not clear yet. This question is more relevant to resource-poor countries, where any reduction of economic burden in acute stroke treatment expected to increase the number of patients undergoing treatment.

Hypothesis:
Direct endovascular thrombectomy is non-inferior to bridging thrombectomy (IV thrombolysis followed by endovascular thrombectomy) for acute stroke patients secondary to anterior circulation large vessel occlusion presenting within 4.5 hours.

Study procedure:

In this prospective study, patients with acute ischemic stroke i.e. anterior circulation stroke satisfying enrolment criteria will be treated with either direct thrombectomy alone or combined treatment i.e. intravenous thrombolysis (IVT) and endovascular treatment. Before starting the reperfusion treatment, relevant baseline information including pre-stroke medical history, history of medications and functional status, time of stroke onset and hospital arrival, severity, time of neuro/vascular imaging, IVT and groin puncture time will be collected.

Considering complication of thrombus fragmentation associated with stent retriever-based mechanical thrombectomy (MT), embolic protection approach will be utilized. Mechanical thrombectomy will be performed by the PROTECT technique i.e. a technical approach combining proximal balloon occlusion together with direct thrombus aspiration.

Intravenous thrombolysis will be done with rTPA i.e. alteplase. Dose of alteplase will be given according to the approved prescribing information i.e. 0.9 mg/kg (not more than 90 mg total dose) infused intravenously over 60 minutes with 10% of the total dose administered as an initial bolus.

Neurological status of the patient will be assessed before treatment and 24 to 36 hours post-treatment. Safety assessment will be done by examination of vital signs of the patients and bleeding episodes. The study will be conducted from Jan 2019 to July 2021.

Outcome measures

Primary outcome: mRS at 90 days.

Secondary outcome: Serious adverse events (sICH/Death/major noncerebral bleeding), mRS shift analysis, NIHSS on day 0, 1 & 2, TICI 2b/3 recanalisation rates on day 0 & 1.

Inclusion Criteria:

1. Age ≥ 18 to < 80 year
2. Neurological deficit with a NIHSS of ≥ 8 and < 30
3. Patient is eligible for intravenous thrombolysis
4. Randomization possible no later than 4 hours 15 minutes after stroke symptom onset and initiation of IV t-PA must be started within 4 hours 30 minutes of stroke symptoms onset.
5. Occlusion (TICI 0-1) of the intracranial internal carotid artery (ICA), the M1 segment of the middle cerebral artery (MCA), or both confirmed by CT or MR angiography
6. Core-infarct volume of Alberta Stroke Program Early CT Score greater than or equal to 6 (≥6) based on baseline CT or MRI

Exclusion Criteria

1. Any contraindication for IV t-PA
2. Pre-treatment with IV t-PA
3. Pregnancy or lactating women.
4. Known (serious) sensitivity to radiographic contrast agents, nickel, titanium metals, or their alloys
5. Renal insufficiency as defined by a serum creatinine > 2.0 mg/dl (or 176.8 µmol/l) or glomerular filtration rate (GFR) < 30 mL/min or requirement for hemodialysis or peritoneal dialysis
6. Severe co-morbid condition with life expectancy less than 90 days at baseline
7. Advanced dementia or significant pre-stroke disability (mRS score of ≥2)
8. Arterial tortuosity, pre-existing stent, other arterial disease and/or difficult femoral access site that would prevent the device from reaching the target vessel and/or preclude safe recovery after

9. CTA or MRA evidence of carotid artery dissection.

Sample Size Calculation:

The distribution of outcome categories is based dichotomised mRS score. A total study size of 550 patients (2 × 275 patients) allows for a power (1-abeta) of 80% at a significance level of 0.05 (alpha), taking into account non-inferiority limit of 10%.

LOI 3:

Title (< 50 Words)	Efficacy and safety of smartphone-based telestroke model for acute stroke treatment.
Background/ Rationale (<150 words)	Early treatment of acute ischemic stroke (AIS) within 4.5 h with intravenous tissue plasminogen activator (tPA) reduces neurological impairment and disability. The earlier it is administered, the better is the effect and the lower is the rate of hemorrhagic complications. Therefore, thrombolysis has become the cornerstone of AIS therapy; however, its widespread use is hindered by a number of obstacles, the most restrictive of which is the narrow therapeutic time window. Yet, thrombolysis with tPA is at present the best available treatment for AIS. Implementing the administration of intravenous thrombolysis in a larger proportion of AIS patients is a major challenge. Telestroke facilities through telemedicine seem to be the "promise," which has the potential to optimize stroke care across all strata, bridging the economic and geographic barriers in the country.
Hypothesis (< 50 words)	Acute stroke treatment provided by smartphone based telestroke model is noninferior to treatment provided by onsite neurologist.
Study Design (<50 words)	It would be a quasiexperimental noninferiority trial to determine whether thrombolysis in acute ischemic stroke patients given after remote consultaton with neurologist on a smartphone based telestroke model is as effective and safe as with onsite presence of neurologist .
Screening/ Inclusion/Exclusion criteria (<200 words)	All adult patients of acute stroke coming within window period at spoke centers and hub centers
Study Procedures (<200 words)	Peripheral centers with 24X7 availability of CT, ECG and blood sugar available will be designated as spoke centers and physicians will be trained in stroke treatment protocol. They will be provided with smartphone devices with appropriate software for Teleconsultation with neurologist. The centers with onsite presence of neurologist will be designated as hub centers. Record of every patient of stroke coming within window period at spoke or hub center would be reviewed by a Telestroke trial review committee which will be blinded to the site of treatment (hub vs spoke) to determine whether treatment decision was

	appropriate or not.
Outcome Measures (<100 words)	The primary outcome measure will be whether the decision to give thrombolytics was appropriate. Secondary outcomes will be rates of thrombolytic use, 90-day outcomes, rates of intracerebral haemorrhage, the completeness of the data, and technical observations.
Sample Size Calculation (<100 words)	Assuming correct decision rate with smartphone Telestroke as 85% and with onsite neurologist as 95% and power of study as 80% at least 60 patients are required in each group.
Statistical Analysis Plan (<100 words)	The Chi square test will be used to compare the correct decision rate (primary study outcome) between treatment groups. A Fisher exact test will be used for all other outcomes, rate of thrombolytic use, rate of intracranial hemorrhage, mortality, and the 90-day modified Rankin scale score (0 to 1 versus 2 to 6)