Clinical Trials in India

ACT Meeting
Quebec City, Oct 2024

Denis Xavier MBBS, MD, MSc (Clin Epi & Biostats)
Professor and Head, Pharmacology
Ex-Vice Dean (PG),
Head, Division of Clinical Research & Training,
St. John's Medical College and Research Institute

Brief notes on India

- Civilization: 3,300 yrs ; Indus, Harappa & Mohanjedaro
  - Metallurgy, Pottery, Underground water & sewage
- Origin of 4 major global religions (23%)
  - Hinduism, Buddhism, Sikhism, Jainism
- Invented zero,
  - Indo-Arabic number system (zero, decimals)
- 2 Indian Epics
  - Couplets: Mahabharata (100,000), Ramayana (24,000)
  - Lines: Homer's Iliad (15,693) & Odyssey (12,110)
- Nalanda University 5th Century, for 1500 years
- Languages: 22; dialects 1,600 (39 major)
- Population: 1.43 billion, world's highest
- GDP: 5th in the world
- Moon club; nuclear capable

Clinical Trials: Quick history

- Before 1990s
  - No multi-centre trials in India
- Few pharma did small studies
- Since 2000, brisk increase in CTs
- Then, things went wrong!

Regulatory

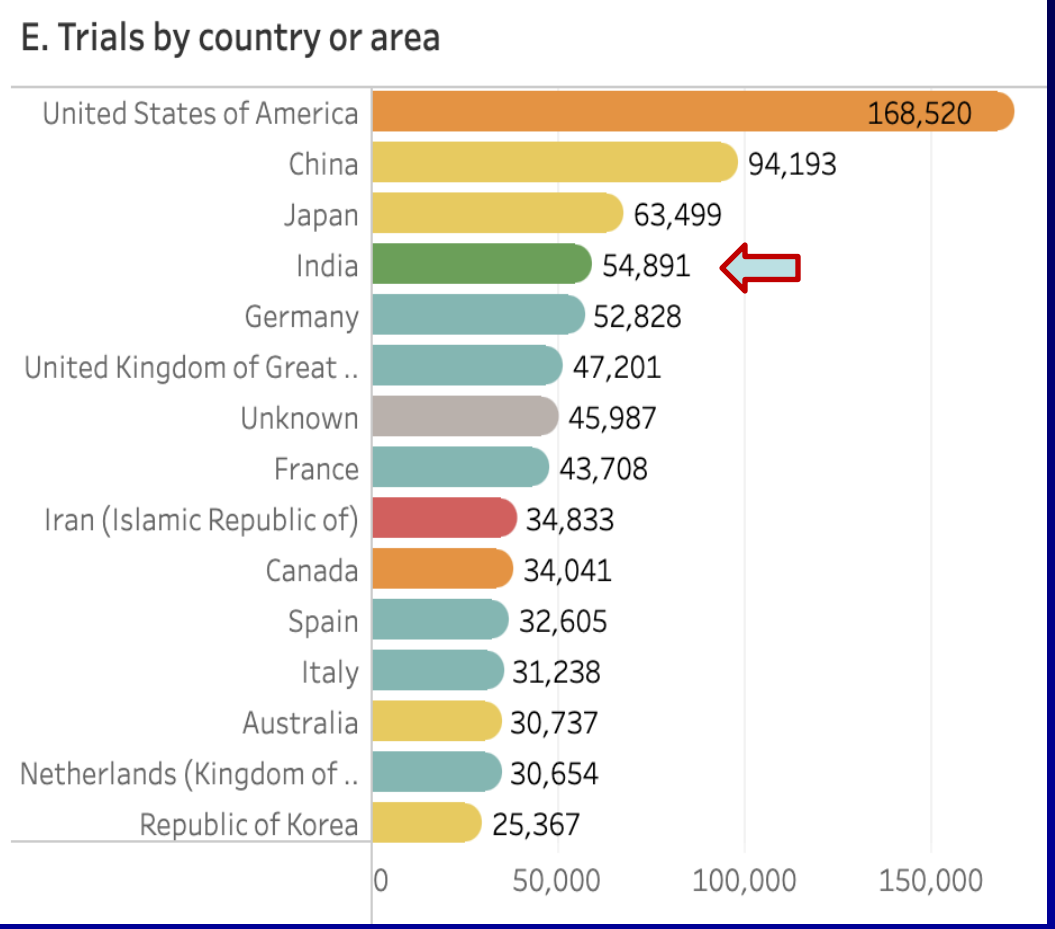
- Prior to 2010
  - Slow approvals, lack of accountability & oversight
- Things went wrong; media and legal issues
- Stringent regulation 2013
  - AV recording of consent
  - Medical management and compensation
    - for all AEs (including trial outcome events)
  - Enrolling in a CT- life long insurance for all illness!
- Trial numbers dropped sharply
  - Even NIH UK – MRC pulled out
  - From approx. 550 in 2010 to <100 (?10)
  - ~80% CROs closed

Academic multi centre trials

- Thanks to
  - Salim Yusuf, 1999, and PJ Deveraux, 2002
- We from St. John's
  - Pioneered acadm large multicenter CTs in India
  - Soon in >100 sites in India; now 230
- Other academic groups in India
  - Diabetes (VM), oncology (CSP), strokes (JP), heart failure (HK), Digital and Primary (DP)
- Government supported
  - BIRAC – CT networks (ophthal, diabetes, rheumatology)
  - ICMR – INTENT (ACCT, DX - PI), others

WHO: Trials Registered since 1999 to 2022 (ICTRP)

World Health Organization | Health Topics | Countries | Newsroom | Emergencies



https://www.who.int/observatories/global-observatory-on-health-research-and-development/monitoring/number-of-trial-registrations-by-year-location-disease-and-phase-of-development
8 Oct 2024

St. John's

Division of
Clinical Research & Training

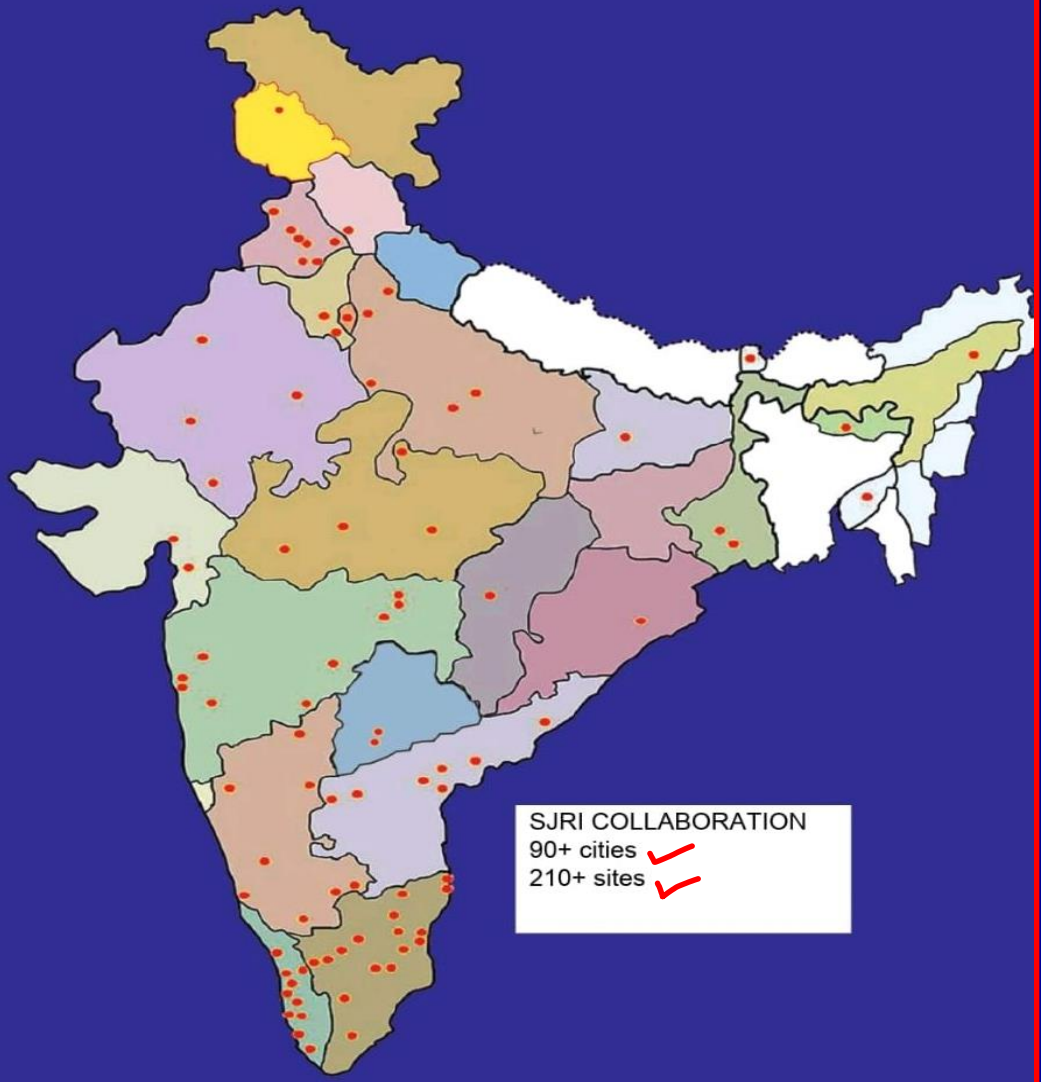
Areas of our work

- Observational studies
  - Cohort, Case Control, Registries
- Randomized Controlled Trials
- Training
  - Health Professionals
  - Research Support Staff

DIVISION OF
CLINICAL RESEARCH & TRAINING

St. John's Medical College Hospital & Research Institute, Bengaluru.

Research Network in India



SJRI: DCRT studies(Swpt 2024)

Designed / coordinated since 1999

OBSv STUDIES

1. ICMR-National C-C in AMI [2,600]
2. INTERHEART [950] [Lancet-04-07, JAMA]
3. CREATE ACS Registry [20,468] [Lancet-08]
4. INTERSTROKE [5,200] [LANCET 2010, 2016]
5. RELY AF Registry, 2,450 [Circl 2016]
6. VISION - 2,008 (JAMA, LANCET…)
7. MACE – 2,000
8. RELLY AF Registry 2050 Circl 2014
9. SPECTRUM 1350
10. FRIENDS 1250
11. OASIS-2 1028
12. EDPS 3200
13. ICMR SRUM 1200

LARGE CLINICAL TRIALS

1. CREATE, 8,060, [JAMA-04, AHJ-04]
2. POISE, 777 [Lancet-08]
3. PRoFESS, 1,620,[NEJM-08x3]
4. OASIS 5, 544[NEJM-06]
5. OASIS 6, 1,450 [JAMA-07]
6. CURRENT, 2300+ [Lancet-10]
7. VITATOPS, 1450+ [Lancet-N-10]
8. RELY, 650 [NEJM - 09]
9. POLYCAP, 2053 **[**Lancet' 09**]**
10. AVVEROES, 200 [NEJM 2011]
11. ARISTOTLE, 650 [NEJM 2011]
12. OASIS-8, 500 [JAMA 2010]
13. APPRAISE – 500 [NEJM 2011]
14. RIVAL – 500 [Lancet-11]
15. HOPE-3, 2,822 [NEJM x 3 2016]
16. MARS – 400 [Blood Pressure 2011]
17. ASPIRE, 400 [NEJM -2014]
18. RECREATE, 250 [Diab Care 2011]
19. INSPIRE – 11,001 (Int J of Stroke 2023)
20. SPREAD-806 (Lancet DE 2016)
21. TIMACS AHA 2008
22. PREPARE – 8,615 (AHJ 2016
23. TIPS-K 650 [Circl Res 2012]
24. FRIENDS-BLR-1,450 [completed]
25. POISE-2 – 595 [NEJMx2]
26. TIPS-3 (Wellcome)- 2,270 (AHJ NEJM `21)
27. SPECTRUM – 1,350
28. ARISTOTLE – 650 (NEJM, LANCET)
29. AVVEROES 203
30. PEGASUS 400
31. ODYSSEY – 600 (NEJM, JACC)
32. DECLARE – 500
33. CANTOS – 600
34. MANAGE – 300 (Lancet 2018)
35. PROGRESS – 3,000
36. AUGUSTUS 400 (Lancet 2019)
37. POISE-3 – 645 [NEJM 2022]
38. IMPACT AF 494 (Lancet 2017)
39. HBS 180
40. PK COVID-19 24
41. ACHIEVE - 500
42. COVID-19 prophyl CS – 1,303 (IJMR 2022)
43. COVID-19 prophyl Coh 12,450 (JAPI 2022)
44. ENRICH-AF – 40 of 100
45. ACT- 300 (Lancet RM 2022]
46. PREDICT – 1100
47. SUPPORT, NCD – 205 of 350
48. Milvexian ACS 750
49. COLT HF 300
50. RADICAL-PC – 500
51. Milvexian AF 350
52. ICMR CAR 41,400

STUDIES TO INITIATE

1. PROSPECT - 1000
2. LEADER-PAD – 1000

Summary: studies and publications

- Studies: 67; participants: ~1,60,400
  - Follow up – 1 month to 7 years
- Key Publications (from approx. 310)
  - Lancet (+fam)- 20+19 = 39
  - NEJM- 17
  - JAMA- 5
  - Am H J – 6
  - Diabetes Care - 2
  - Circulation- 10
  - Eur H J-2

Study Medications Management

Sl no	Study	Patients	Packages	Units	Years	Sites
1	CREATE	8060	12,000	1,41,050	3	57
2	POISE-1	777	800	2,91,375	2.5	24
3	VITATOPS	1421	21,107	22,16,760	5	23
4	HOPE 3	2822	2040	1,44,20,420	7	24
5	ASPIRE	400	3400	43,800	3	20
6	MARS	400	7250	48,000	2	11
7	POISE-2	595	1132	35,700	3	17
8	ACHIEVE*	300	805*	27,300	5	21
9	ACT	70	104	2,400	1	11
10	PROFESS	1620	7100	47,30,400	5	30
11	MANAGE	250	1372	1,82,500	3	12
12	RECREATE	273	815	8190	2	18

Indirect Study Drugs Management

1. POISE 3 - 645
2. TIPS 2 - 518
3. OASIS 5, 544
4. OASIS 6, 1,450
5. CURRENT, 2300
6. TIPS 3 - 2739
7. VITATOPS, 1,450
8. RELY, 650
9. POLYCAP, 2053
10. AVVEROES, 200
11. ARISTOTLE, 650
12. OASIS-8, 500
13. APPRAISE – 500

Equipment and Study Materials

- 3,73,204 Units for 27 studies, 691 sites
- Equipment:
  - digital BP machines, mobile phones, tablets, weighing scales, measuring tapes, height measurement scale, handgrip measure, glucometers with strips & needles, point of care devices, blood sample collection kits, warm oxygen therapy machines, spring scales for waist hip measurement, body composition monitor thermometers.
- Study material:
  - Case report forms, questionnaires, patient files, site files, informed consent forms including translations, participant diaries, cards, study posters, education materials, manuals, calendars.

New Regulations

- NDCT 2019
  - New Drugs and Clinical Trials rules
- Clarified
  - Academic and Regulatory trials
  - Academic trials no Regl approval (EC, CTRI ✓)
  - Compensation, medical management (rational)
- HMSC
  - Approves international academic research collaborations

New Drugs & Clinical Trial Rules 2019

रजिस्ट्री सं० डी० एल०-33004/99

REGD. NO. D. L.-33004/99

भारत का राजपत्र
The Gazette of India

असाधारण

EXTRAORDINARY

भाग II—खण्ड 3—उप-खण्ड (i)

PART II—Section 3—Sub-section (i)

प्राधिकार से प्रकाशित

PUBLISHED BY AUTHORITY

सं. 200] नई दिल्ली, मंगलवार, मार्च 19, 2019/फाल्गुन 28, 1940

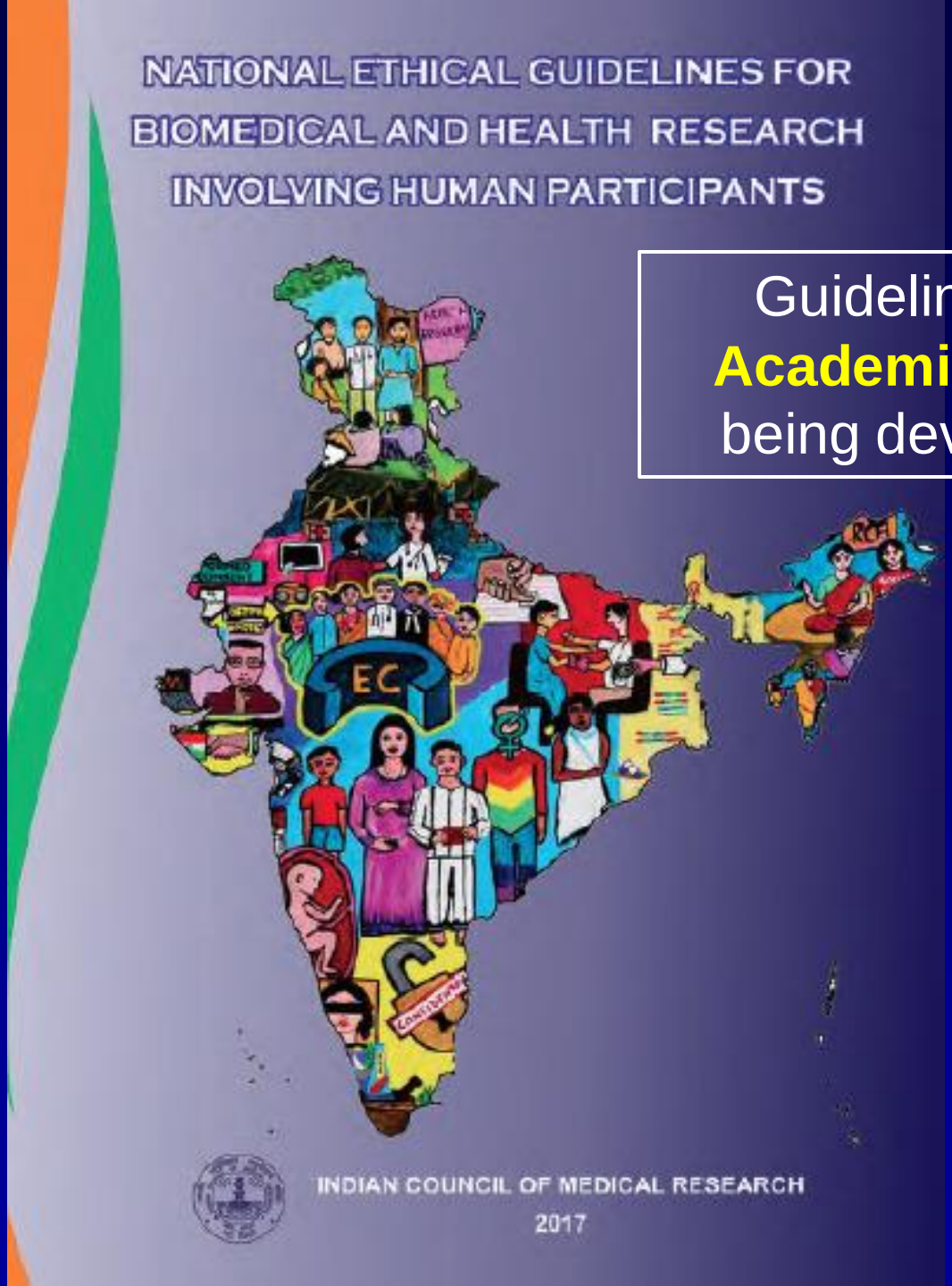
No. 200] NEW DELHI, TUESDAY, MARCH 19, 2019/ PHALGUNA 28, 1940

Academic clinical trial

- Means a clinical trial of a drug
  - Already approved for a certain claim
- Initiated by
  - Investigator, academic or research institution
- For a
  - New indication or new route of administration or new dose or new dosage form
- Where results are intended to be used
  - Only for academic or research purposes
- **Not for**
  - Seeking approval for marketing or commercial purpose.

Academic clinical trials: 2 definitions

- Global academic trials
  - Part of an international study
  - Usually initiated outside India
  - Sponsor
    - University/ research institute
    - NOT pharma
- Local academic trials
  - Initiated in India
  - Sponsor
    - University/ research institute
    - NOT pharma



Guidelines for
Academic Trials
being developed

GUIDELINES SERIES-III

GENERAL GUIDELINES FOR CLINICAL EVALUATION OF AYURVEDIC INTERVENTIONS

CENTRAL COUNCIL FOR RESEARCH IN AYURVEDIC SCIENCES
Ministry of AYUSH, Government of India
New Delhi

Steps for conducting

- Global academic CTs
- Local academic CTs

Steps: Global academic CT

- Need
  1. Ethics approval – follow ICMR guidelines
  2. CTRI registration
  3. HMSC approval
  4. Import license
  5. Insurance
  6. Compensation/ medical mgmnt plans/ funds
  7. SAE reporting to sponsor and EC
- No need for
  - DCGI approval
  - SAE reporting to Regulators

Steps: Local academic CT

- Need
  1. Ethics approval – follow ICMR guidelines
  2. CTRI registration
  3. ~~HMSC approval~~
  4. ~~Import license~~
  5. Insurance
  6. Compensation/ medical mgmnt plans/ funds
  7. SAE reporting to sponsor and EC
- No need for
  - DCGI approval
  - SAE reporting to Regulators (but report to sponsor and ECs)

HMSC approvals

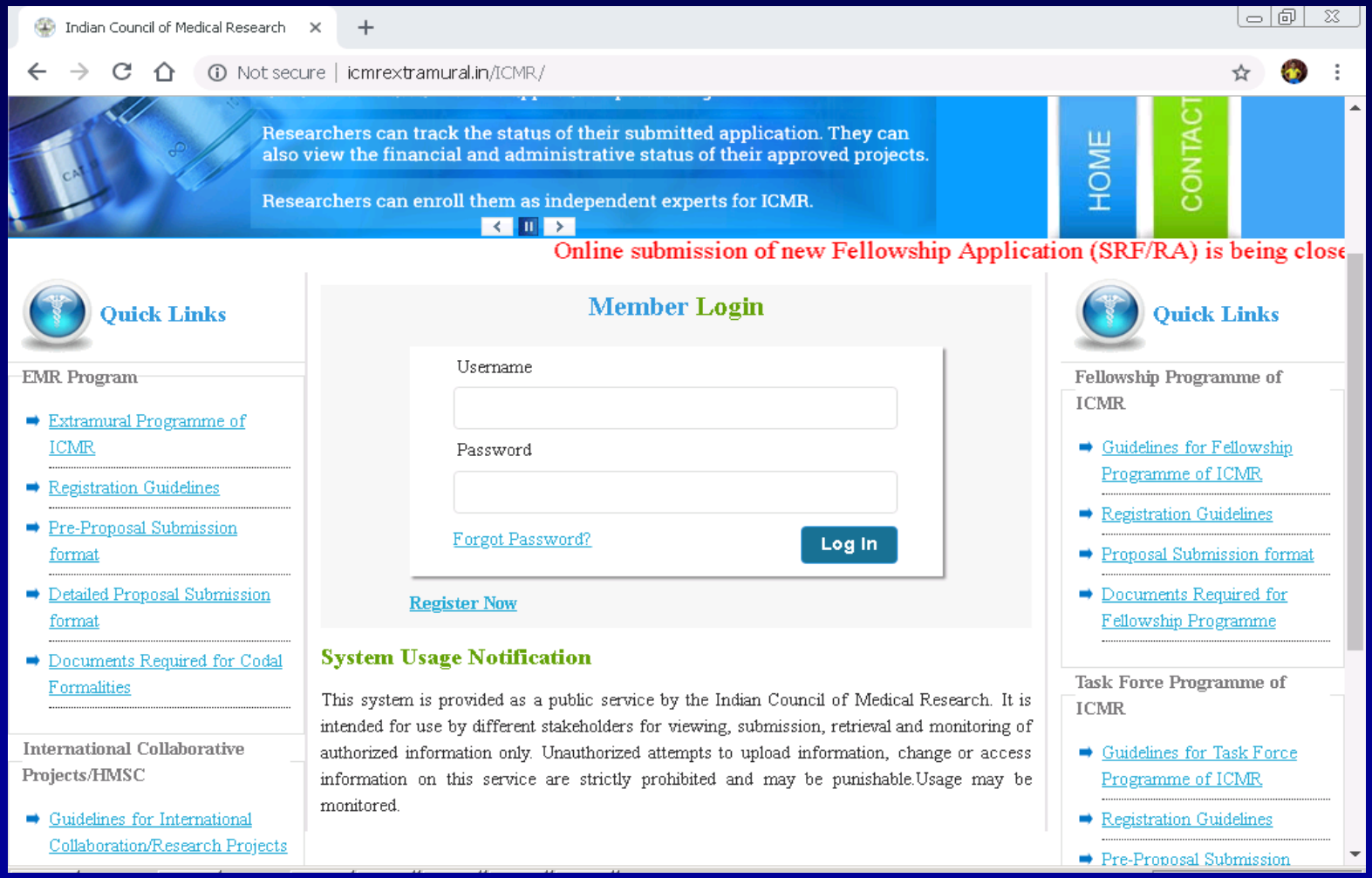
- Documents for submission online
  1. Research proposal
  2. ICMR summary sheet
  3. Material transfer agreement (if applicable)
  4. Protocol
  5. ICF
  6. Letter from foreign collaborator
  7. If multi centre - ethics approval 50% sites
  8. DCGI approval, if applicable
  9. Drug import licence
  10. CTRI registration (ref # during application)

Health Ministry Screening Committee (HMSC)
Approval for Academic studies

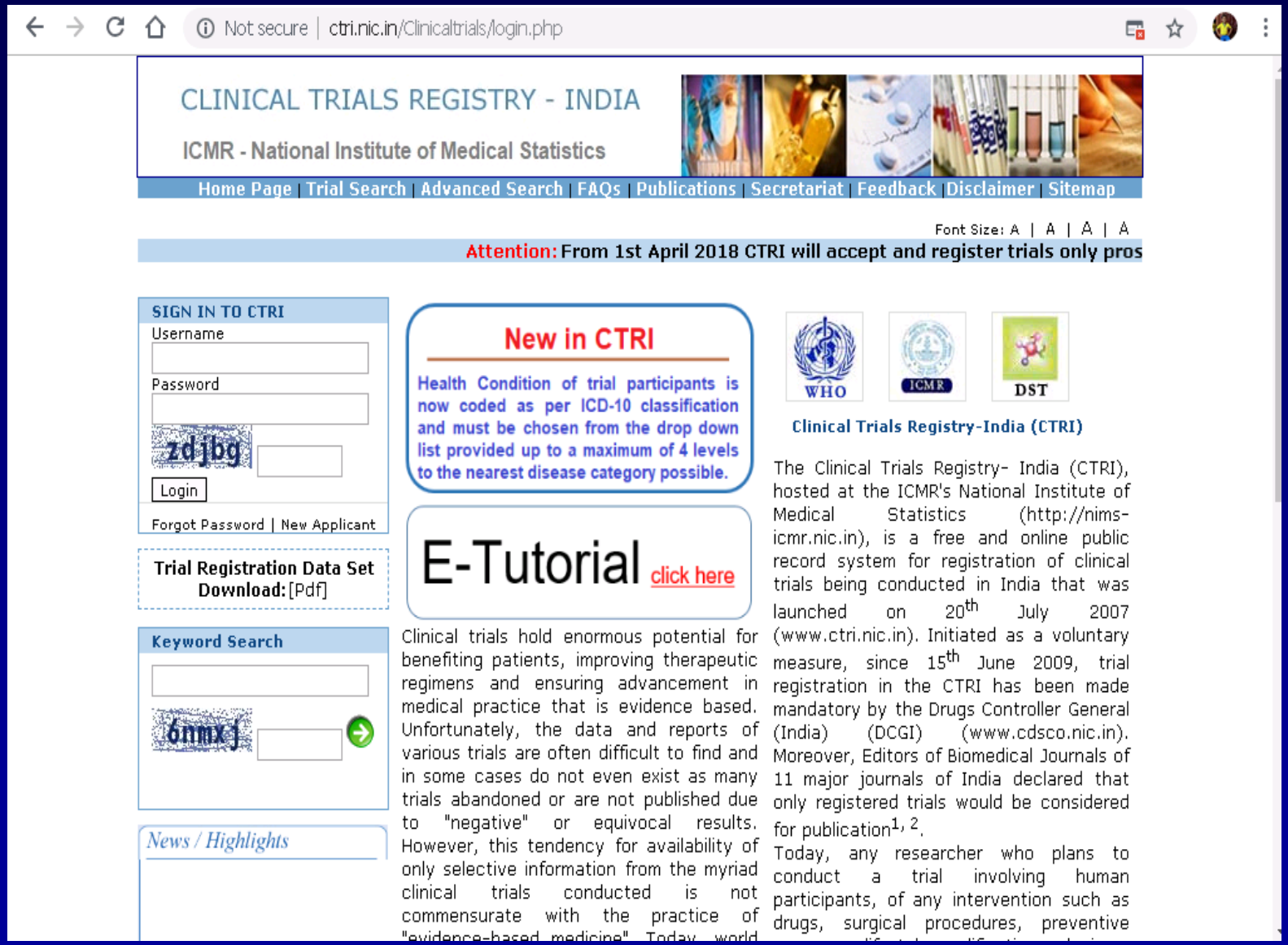
HMSC approval for Academic Trials

- Guidelines formulated by ICMR
  - Covers pharmaceuticals, biologicals, non allopathic
  - Also non interventional studies
  - Last release in 2017

ICMR website for HMSC application submission Portal



CTRI website



SUGAM Portal

- An online web portal from CDSCO effective from Jan 2019
- Can apply for :
  - NOCs, licenses, registration certificates, permissions & approvals.
- Applicants can track
  - their applications, respond to queries and download the permissions issued by CDSCO.
- Enables CDSCO officials to:
  - process the applications online and generate the permissions online and generate MIS reports.

SUGAM portal login

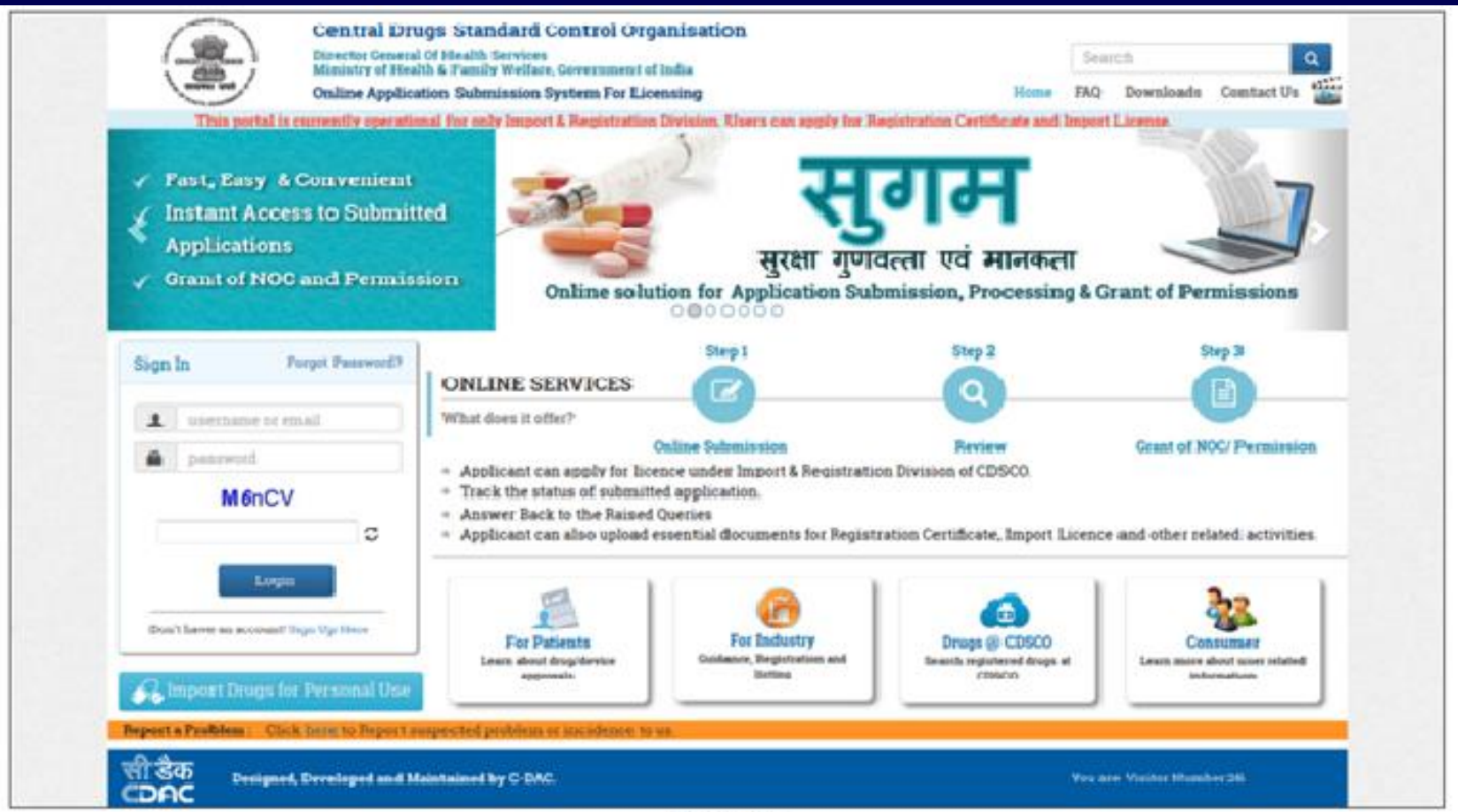


Figure 1.1

NDCT-2019
Compensation & Medical Management

Rule	Title for compensation in case of injury during clinical trials BA/BE study of new drug or IND	Change made in the new drug and clinical trial rules 2019

SEVENTH SCHEDULE

(See rules 39, 40, and 42)

FORMULAE TO DETERMINE THE QUANTUM OF COMPENSATION IN THE CASES OF CLINICAL TRIAL RELATED INJURY OR DEATH

1. Formula in case of clinical trial related death:

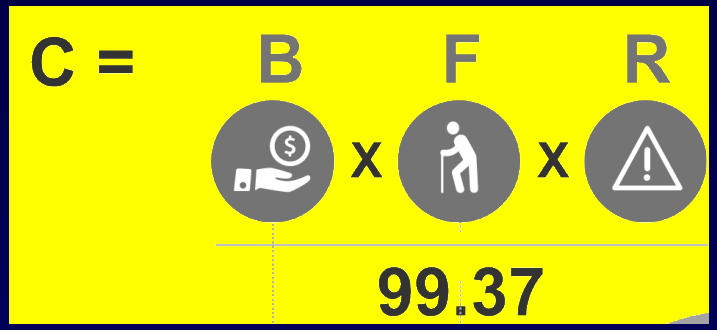
Compensation = (B x F x R) / 99.37

Where,

B = Base amount (i.e. 8 lacs)

F = Factor depending on the age of the trial subject as per Annexure 1 (based on Workmen Compensation Act)

R = Risk Factor depending on the seriousness and severity of the disease, presence of co-morbidity and duration of disease of the trial subject at the time of enrolment in the clinical trial between a scale of 0.5 to 4 as under:



B: Base amount = 8.0L
F: Factor related to age
R: Risk factor (0.5 X 4.0)

Risk Factor

0.5: Terminally ill patients (expected survival not more than 6 months)
1.0: Patient with high risk (expected survival between 6 - 24 months)
2.0: Patient with moderate risk
3.0: Patient with mild risk
4.0: Healthy volunteers or subject to no risk

Compensation = 2 X W X N.

Where,

W = Minimum wage per day of the unskilled worker (in Delhi)

N = Number of days of hospitalization

Annexure 1

Factor (F) for calculating the amount of compensation

Age Not more than…	Factor
16	228.54
17	227.49
18	226.38
19	225.22
20	224.00
21	222.71
22	221.37
23	219.95
24	218.47
25	216.91
26	215.28
27	213.57
28	211.79
29	209.92
30	207.98
31	205.95
32	203.85
33	201.66
34	199.40
35	197.06
36	194.64
37	192.14
38	189.56
39	186.90
40	184.17

Case Scenarios:

Age (Years)	USD/INR	R = 4	R = 3	R = 2	R = 1	R = 0.5
65						
35						
18						

Medical Management & Compensation

IP Management

- Regulatory issues for importation
- Import license
  - Drugs Controller General of India and
  - Director General of Foreign Trade -

St. John's Medical College & Research Institute

Bengaluru, India

In Collaboration with faculty from McMaster University, Canada

15th Annual International One-week Course on

Health Research Methodology and Evidence Based Medicine

March 11th to 15th, 2024

CME Credits for eligible candidates

Topics:

Methods in

- Randomized Controlled Trials
- Observational Studies (Cross Sectional, Case Control and Cohort)
- Systematic Reviews & Meta-analysis
- Qualitative Studies
- Registries
- Real World Evidence studies

- Evidence Based Medicine
  - Origin, Principles, Clinical Practice and Future
- Research Publications
- Grants Writing
- Operational & Regulatory
  - Human Research Ethics
  - Regulatory Issues
  - Project management
  - Budgeting

- Health Policy and Knowledge Translation
- Data Management
- Hands-on Statistical analysis on SPSS
- Biostatistics
  - Parametric tests
  - Non-parametric tests
  - Correlation & Regression
  - Survival Analysis

St. John's Medical College & Research Institute

Bengaluru, India

ICMR INTENT Advanced Centre for Clinical Trials

In Collaboration with faculty from

McMaster University, Canada and Duke University, USA

4th Annual One-week Course on

Randomized Controlled Trials

Oct 21st to 25th, 2024

CME Credits for eligible candidates – Applied for KMC Credits

Topics:

RCT Designs & Analysis

- RCT : key concepts
- Cluster RCT
- Factorial trials
- Non-inferiority trials
- Adaptive trials
- Expertise based trials
- Stepped wedge trials
- Implementation trials
- Community based trials
- Real world and Pragmatic trials

Interventions:

- Drugs/ devices/ surgical
- Complex Behavioural

Statistics:

- Sample size for different RCT designs
- Parametric & Non-parametric tests
- Mixed linear models
- Survival analysis

Techniques:

- Randomization
- Blinding
- Allocation concealment
- Investigational Product Management

Operations and Regulatory:

- Regulatory Issues
- Documentation/ manuals
- Data management
- Adjudication
- Budgets
- Insurance/Compensation

A workshop on

Implementation Science Research (ISR)

A Diamond Jubilee Event

CAREADD & DCRT

St. John's Medical College & Research Institute, Bengaluru

October 4th and 5th, 2023, 9.00 am to 7.00 pm
4 CME Credits awarded

CONVENOR:
Dr Denis Xavier, St. John's Medical College (SJMC)

WORKSHOP DIRECTORS
Dr. Sowmyashree M Kaku, St. John's Research Institute (SJRI)
Dr. Kavita Singh, Public Health Foundation of India (PHFI)

- **Implementation Science Research aims to develop evidence on effective and sustained uptake of proven interventions.**
- **While this kind of research is very important for countries like India, unfortunately it is less common.**

Key highlights

- Why do some evidence-based treatments not work in the community?
- How do we get "what works" to the people who need it, with greater speed, fidelity, efficiency, and quality?
- Do we need different methods or study designs to evaluate the impact of implementation strategies?
- How to ensure the sustainability of proven health interventions?
- How do I apply for implementation science grants?

Who can attend?

Early to mid-career medical researchers including but not limited to medical, nursing, dental, pharmacy, ethics committee, regulators, policy, social scientists, health economists, etc.

Benefits:

- Identify relevant implementation science research topics
- Use appropriate theoretical models, designs and research
- Collaborate within India and globally
- Translate your research findings into policy and practice

Methodology:

Crisp interactive lectures, facilitator-led small group sessions, project development, and group presentations.

TOPICS

- Models, Frameworks and Theories
- Key concepts and issues for ISR
- Operationalizing ISR
- Stakeholder engagement
- Case studies
- ISR in the real world
- Funding for ISR research

FACULTY*

- Prof. D Prabhakaran, PHFI, Gurugram
- Prof. Monika Arora, PHFI, Gurugram
- Prof. Mark Huffman, WU, USA
- Prof. Denis Xavier, SJMC, Bangalore
- Dr. Jeemon P, SCTIMST, Trivandrum
- Dr. Kavita Singh, PHFI, Gurugram
- Dr. D Praveen, George Institute, India

* List of faculty is prefinal

To register click here –
https://bit.ly/SJMCRI_IRW2023

Trials in India

Opportunities

- Large population and disease burden
- Heterogenous,
  - including drug naïve
- 60,000 hospitals (62% Pvt)
- 700+ medical college hospitals
- All physicians
  - English speaking
- Streamlined regulations
  - NDCT 2019
  - Including simplifying for academic trials

Challenges

- Residual suspicion on trials:
  - patients and media
- Translations
  - informed consent & other patient documents:
  - 9 to 12 major languages
- Ethics and contracting
  - Challenging in a few sites
- CROs and SMOs
  - Profit oriented
  - Complicating processes

Conclusions

- Huge scope for more local trials
- And …
- Good time to do trials in India!