

Randomized Clinical Trials in Resource Limited Settings – Challenges and Solutions

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Objectives

What are Randomized Controlled Trials

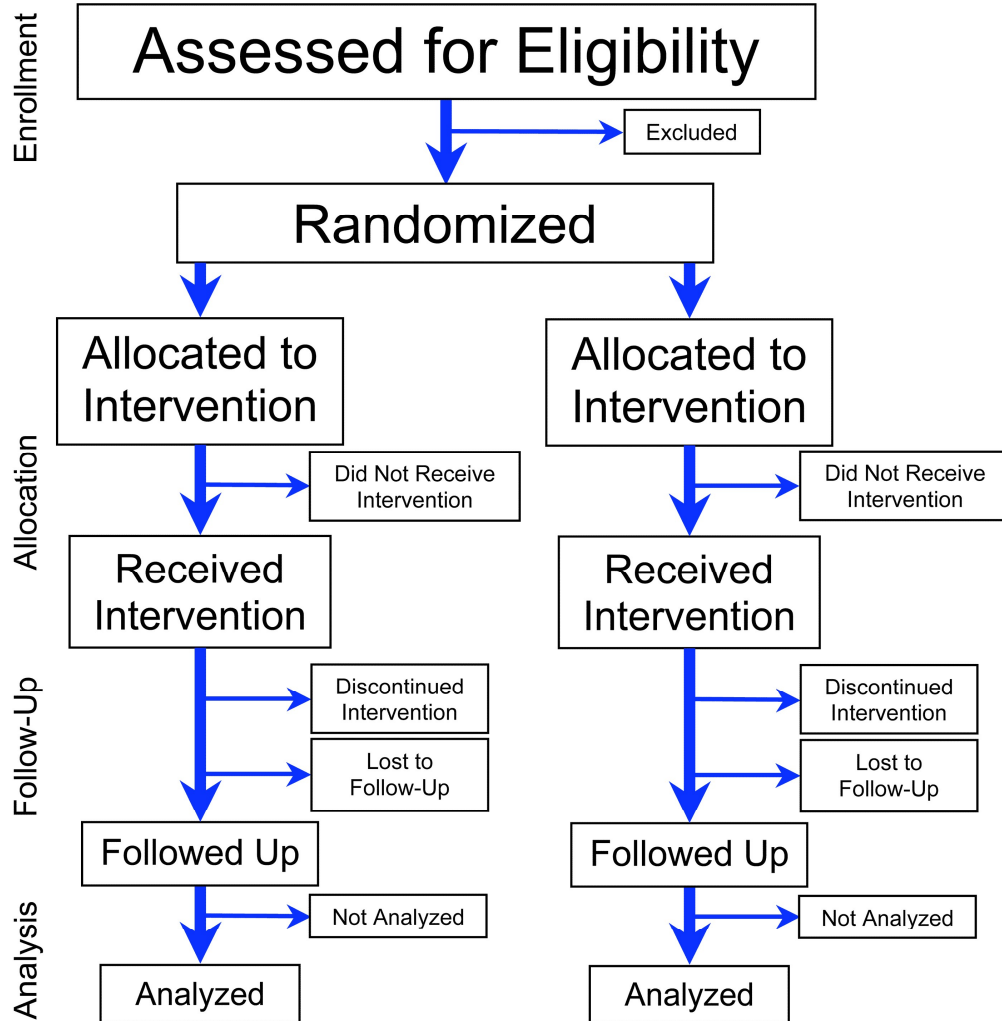
Why is conducting RCTs difficult

Special considerations for resource limited settings

Possible ways to overcome barriers

Randomized Controlled Trials

- Holy grail of clinical research – Gold standard
- Form the basis for meta-analysis – highest form of evidence
- The important components are –
 - *Prospective design*
 - *Random allocation*
 - *Controlled by a pre-designed protocol*
 - *Removing bias as far as possible*



RCT Design

Why are RCTs the gold standard?

Randomly allocate subjects to one of the arms, eliminating selection bias

Blinding improves the quality

Randomisation also effectively eliminates confounders

Well designed protocol ensures that results are meaningful and applicable to desired population

Types of RCTs

- Blinded (Single/Double/Triple) or Open-label
- Placebo controlled or comparing different interventions
- Single centre or multi-centre
- Superiority, Equivalence or Non-inferiority
- Parallel group or Crossover

Why are RCTs challenging?

- Prior data required for optimal sample size
- Randomization precludes RCTs for potentially harmful interventions
- Ideal placebo is hard to formulate
- Costs and infrastructural limitations
- Coordination in multicenter trials
- High dropout rate in the event of side effects/lack of incentive

How do some RCTs go wrong?

Unclear hypotheses and multiple objectives

Poor selection of endpoints

Inappropriate subject selection criteria

Non-clinically relevant or feasible

treatment/intervention

Inadequate randomisation, stratification, blinding

Lack of stratification in small RCTs

Insufficient sample size/power

Failure to anticipate common practical problems

Challenging issues in randomised controlled trials

A.D. Nichol^{a,b,*}, M. Bailey^a, D.J. Cooper^{a,b}

On behalf of the POLAR and EPO investigators¹

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^bAlfred Hospital, Melbourne, Victoria 3004, Australia

Lack of Statistics Training

LITTLE EMPHASIS ON TRAINING IN BIOSTATISTICS
DURING MEDICAL TRAINING

MEDICAL TRAINING DOES NOT STRESS UPON
IMPORTANCE OF STATISTICS AND CLINICAL RESEARCH

LACK OF EXPERTISE IN BIOSTATISTICS

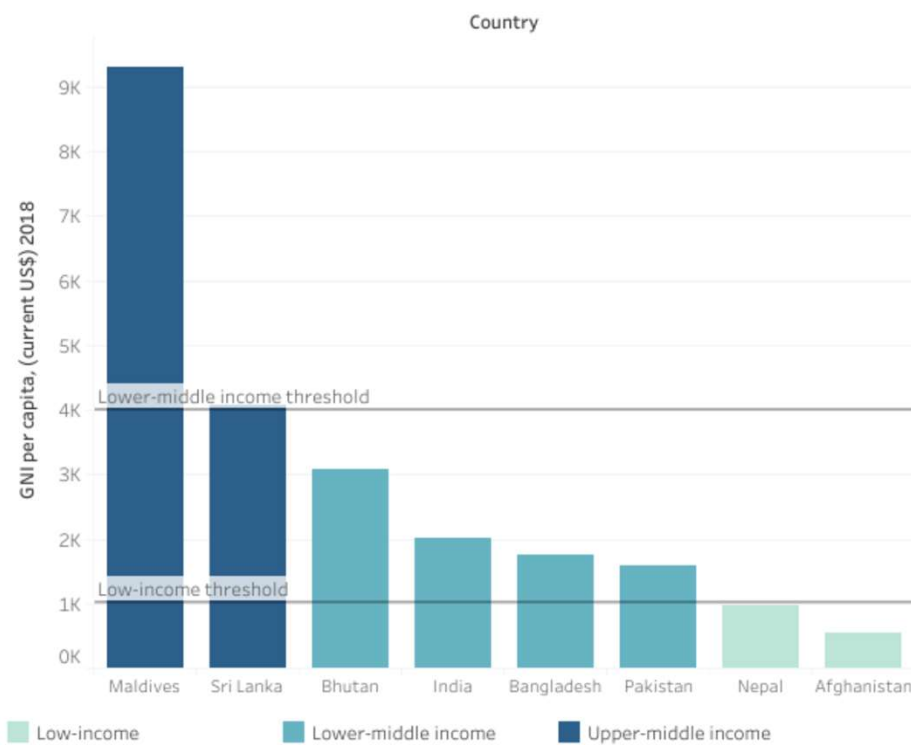
NO DEDICATED STATISTICIANS IN MOST
DEPARTMENTS

LACK OF FUNDING TO OUTSOURCE STATISTICAL
ANALYSES AND STUDY DESIGNS



Resource Limited Settings

Classification Of South Asian Countries By Income Levels, 2019-20

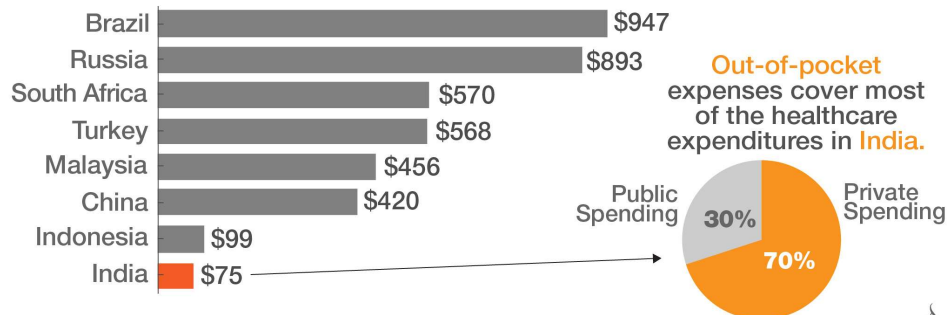


**India – A
Resource
Limited Setting**

Economics of Healthcare in India

Health expenditure per person

Among the BRICS and other newly industrialised nations, India spends the least on health per capita.

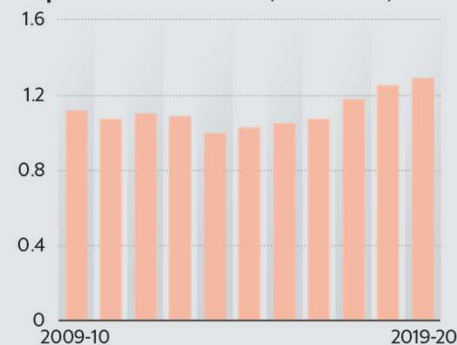


Source: World Health Organization

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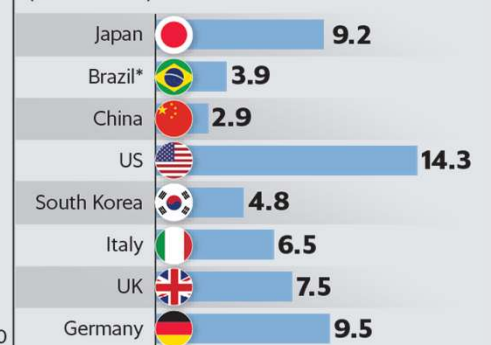
India's public health expenditure was just 1.29% of GDP in 2019-20. In 2018 too, the country lagged behind BRICs peers as well as developed nations.

India's (centre plus states) public expenditure on health (as % of GDP)



Source: National Health Profile 2019, Government of India; CARE Ratings' calculations

Public expenditure on health in 2018 (as % of GDP)



*For 2017

Source: OECD, Conta-Satélite de Saúde

Special Challenges

| Thematic barriers | Sub-themes |
|---|--|
| Lack of financial and human capacity | Lack of funding Lack of skilled personnel Lack of awareness and motivation |
| Ethical and regulatory system obstacles | Delay of approval decisions Unskilled authorities Complex and strict ethical and regulatory system |
| Lack of research environment | Lack of infrastructure Lack of research materials/facilities Lack of conducive scientific atmosphere |
| Operational barriers | Unsupportive administrative system Lack of/difficult patient recruitment |
| Competing demands | Lack of time Other competing priorities |

Alemayehu et al. *International Journal for Equity in Health* (2018) 17:37
<https://doi.org/10.1186/s12939-018-0748-6>

International Journal for
Equity in Health

SYSTEMATIC REVIEW

Open Access

Barriers for conducting clinical trials in developing countries- a systematic review

Chalachew Alemayehu^{1*}, Geoffrey Mitchell¹ and Jane Nikles²



The Indian Scenario

- Uneducated population – Do not understand consent
- Spotlight over financial benefits to researchers
- Lack of a national ethics/regulatory body
- A costly drug tested in India may not be affordable locally
- Lack of representation of patient groups on committees
- Overburdened healthcare system – Lack of time for research

Strengthening clinical research in India

THE LANCET

The way forward

- Interdepartmental and Interfacility collaborations
- Development of skilled manpower
- Setting up of a regulatory body and operational framework
- Simplifying application and approval process – transparency
- Remove restrictions while keeping necessary checks
- Incorporate trials into routine clinical practice
- Robust Electronic Medical Record keeping systems
- Strengthen primary healthcare and empowering research facilities
- Experienced centers need to take up mentorship roles



**Lessons from the
past – How we
overcame barriers**

Randomized Controlled Trial Comparing Cerebral Perfusion Pressure–Targeted Therapy Versus Intracranial Pressure–Targeted Therapy for Raised Intracranial Pressure due to Acute CNS Infections in Children*

Ramesh Kumar, MD, DM; Sunit Singhi, MD; Pratibha Singhi, MD; Muralidharan Jayashree, MD; Arun Bansal, MD; Anuj Bhatti, MD, DM

| Challenges | Solutions |
|------------------------------|--|
| Lack of Financial Capacity | Institute funded research |
| Lack of Human Skill | Coordination with Neurosurgery, Hands on training of PICU fellows |
| Ethical Obstacles | Thorough literature review and ethical justification |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |

Original Investigation

Low-Dose vs Standard-Dose Insulin in Pediatric Diabetic Ketoacidosis

A Randomized Clinical Trial

Karthi Nallasamy, MD, DM; Muralidharan Jayashree, MD; Sunit Singhi, MD; Arun Bansal, MD

JAMA Pediatrics

| Challenges | Solutions |
|------------------------------|--|
| Lack of Financial Capacity | Institute funded research, Simple design, No costly interventions |
| Lack of Human Skill | No skill based intervention |
| Ethical Obstacles | Thorough literature review and ethical justification |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |

ORIGINAL ARTICLE

Airway Pressure Release Ventilation in Pediatric Acute Respiratory Distress Syndrome

A Randomized Controlled Trial

Saptharishi Lalgudi Ganesan¹, Muralidharan Jayashree¹, Sunit Chandra Singhi^{1,2}, and Arun Bansal¹

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**American Journal of Respiratory
and Critical Care Medicine**

| Challenges | Solutions |
|------------------------------|---|
| Lack of Financial Capacity | Institute funded research |
| Lack of Human Skill | Training through classes on APRV, Clear objective protocol for use of intervention |
| Ethical Obstacles | Thorough literature review and ethical justification, A priori planned interim analysis |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |

Evaluation of Effect of Probiotics on Cytokine Levels in Critically Ill Children With Severe Sepsis: A Double-Blind, Placebo-Controlled Trial*

Suresh K. Angurana, DM, MNAMS, FCCP¹; Arun Bansal, MD, MAMS, FCCM¹;
Sunit Singhi, MD, FIAP, FAMS, FISCCM, FICCM, FCCM^{1,2}; Ritu Aggarwal, MD³;
Muralidharan Jayashree, MD, FIAP¹; Manila Salaria, MSc, PhD³; Navdeep K. Mangat, MSc³




| Challenges | Solutions |
|------------------------------|---|
| Lack of Financial Capacity | Use of departmental grants |
| Lack of Human Skill | Bio-assays done with an ongoing project in Dept of Experimental Medicine, Good interdepartmental coordination |
| Ethical Obstacles | Thorough literature review and ethical justification, Simple, cheap, potentially harmless intervention |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |

Randomized Clinical Trial of 20% Mannitol Versus 3% Hypertonic Saline in Children With Raised Intracranial Pressure Due to Acute CNS Infections*

Ramachandran Rameshkumar, MD, DNB, DM; Arun Bansal, MD; Sunit Singhi, MD; Pratibha Singhi, MD; Muralidharan Jayashree, MD

Pediatric Critical Care Medicine

Society of
Critical Care Medicine
The International Society of Pediatric Critical Care Medicine

 World Federation of
Pediatric Intensive and
Critical Care Societies

| Challenges | Solutions |
|------------------------------|--|
| Lack of Financial Capacity | Institute funded research, Low-cost interventions |
| Lack of Human Skill | No special skilled intervention |
| Ethical Obstacles | Thorough literature review and ethical justification |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |



**Lessons from the
past – Where we
faltered**

Steroids in ARDS Study (Unpublished)

| Challenges | Remarks |
|------------------------------|--|
| Study Design | Underestimated mortality from ARDS, Sample size too large for available time |
| Lack of Financial Capacity | Institute funded research, No costly intervention |
| Lack of Human Skill | No skilled intervention involved |
| Ethical Obstacles | Thorough literature review and ethical justification |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff |
| Competing Demands | Incorporated into clinical practices |

Status Epilepticus Study (Unpublished)

| Challenges | Remarks |
|------------------------------|--|
| Study Design | Sample size too large for available time |
| Lack of Financial Capacity | Institute funded research, No costly intervention |
| Lack of Human Skill | No skilled intervention involved |
| Ethical Obstacles | Thorough literature review and ethical justification |
| Lack of Research Environment | Conducted at a teaching research hospital |
| Operational Barriers | Robust protocol, Prior sensitization of staff, Difficulty and Delay in forming ideal placebo and concealed drugs |
| Competing Demands | Incorporated into clinical practices |

The image features a complex wooden maze constructed from light-colored wooden sticks, set against a dark, textured wooden background. A large, semi-transparent light blue circle is centered over the maze. Inside this circle, the text "Where there is a will, there is a way!" is written in a bold, black, sans-serif font, arranged in four lines.

**Where there is a
will, there is a
way!**

TABLE 3. Ten Most Influential Centers Ranked by Four Different Measures of Influence

| Rank | Researchers | Published RCTs | Total Times RCTs Cited | Collaborating Centers |
|------|--|--|---|---|
| 1 | Children's Medical Center Dallas—USA (42) | Children's Medical Center Dallas—USA (20) | Children's Medical Center Dallas—USA (2,152) | Children's Medical Center Dallas—USA (181) |
| 2 | Children's Hospital of Pittsburgh—USA (38) | PGIMER—IND (17) | Hospital for Sick Children—CAN (1,847) | Children's Hospital of Pittsburgh—USA (172) |
| 3 | Universidade de So Paulo—BRA (37) | Children's National Medical Center—USA (16) | Children's Hospital of Pittsburgh—USA (1,602) | Hospital for Sick Children—CAN (168) |
| 4 | Erasmus Medical Center—NLD (36) | Hospital for Sick Children—CAN (16) | Children's Hospital of Philadelphia—USA (1,377) | Children's Hospital of Philadelphia—USA (157) |
| 5 | Boston Children's Hospital—USA (29) | Universidade de So Paulo—BRA (16) | Children's Hospital of Michigan—USA (1,300) | Primary Children's Medical Center—USA (142) |
| 6 | Hospital for Sick Children—CAN (29) | Children's Hospital of Pittsburgh—USA (15) | Texas Children's Hospital—USA (1,190) | Children's National Medical Center—USA (126) |
| 7 | Royal Children's Hospital—AUS (29) | Cincinnati Children's Hospital—USA (14) | Primary Children's Medical Center—USA (1,180) | Children's Hospital of Michigan—USA (125) |
| 8 | Golisano Children's Hospital—USA (28) | Children's Hospital of Philadelphia—USA (13) | Stollery Children's Hospital—CAN (1,172) | Phoenix Children's Hospital—USA (123) |
| 9 | All India Institute of Medical Sciences—IND (27) | Primary Children's Medical Center—USA (13) | Great Ormond Street Children's Hospital—GBR (1,167) | Stollery Children's Hospital—CAN (116) |
| 10 | PGIMER—IND (27) | Boston Children's Hospital—USA (12) | Children's National Medical Center—USA (1,165) | Great Ormond Street Children's Hospital—GBR (114) |

Research Collaboration in Pediatric Critical Care Randomized Controlled Trials: A Social Network Analysis of Coauthorship*

Mark Duffett, PhD^{1,2}; Melissa Brouwers, PhD³; Maureen O. Meade, MD, MSc^{3,4}; Grace M. Xu, BHSc⁵; Deborah J. Cook, MD, MSc^{3,4}

Take Home Message

CONDUCTING RCTS IS
CHALLENGING

HIGH QUALITY RCTS
CAN BE CONDUCTED IN
RESOURCE LIMITED
AREAS

INNOVATIVE, COST
EFFECTIVE, ROBUST
STUDY DESIGNS
ESSENTIAL

MULTIDISCIPLINARY
COLLABORATIONS ARE
THE NEED OF THE
HOUR

LEARN FROM THE PAST
AND KEEP AT IT