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IMPLEMENTING A CLINICAL STUDY IN LOW RESOURCES SETTINGS

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- Overview of conducting clinical research in low resource settings
- Other contentious issues and considerations in the implementation of clinical research in low resource settings
- Conclusion

Lecture goal and Objectives

Goal

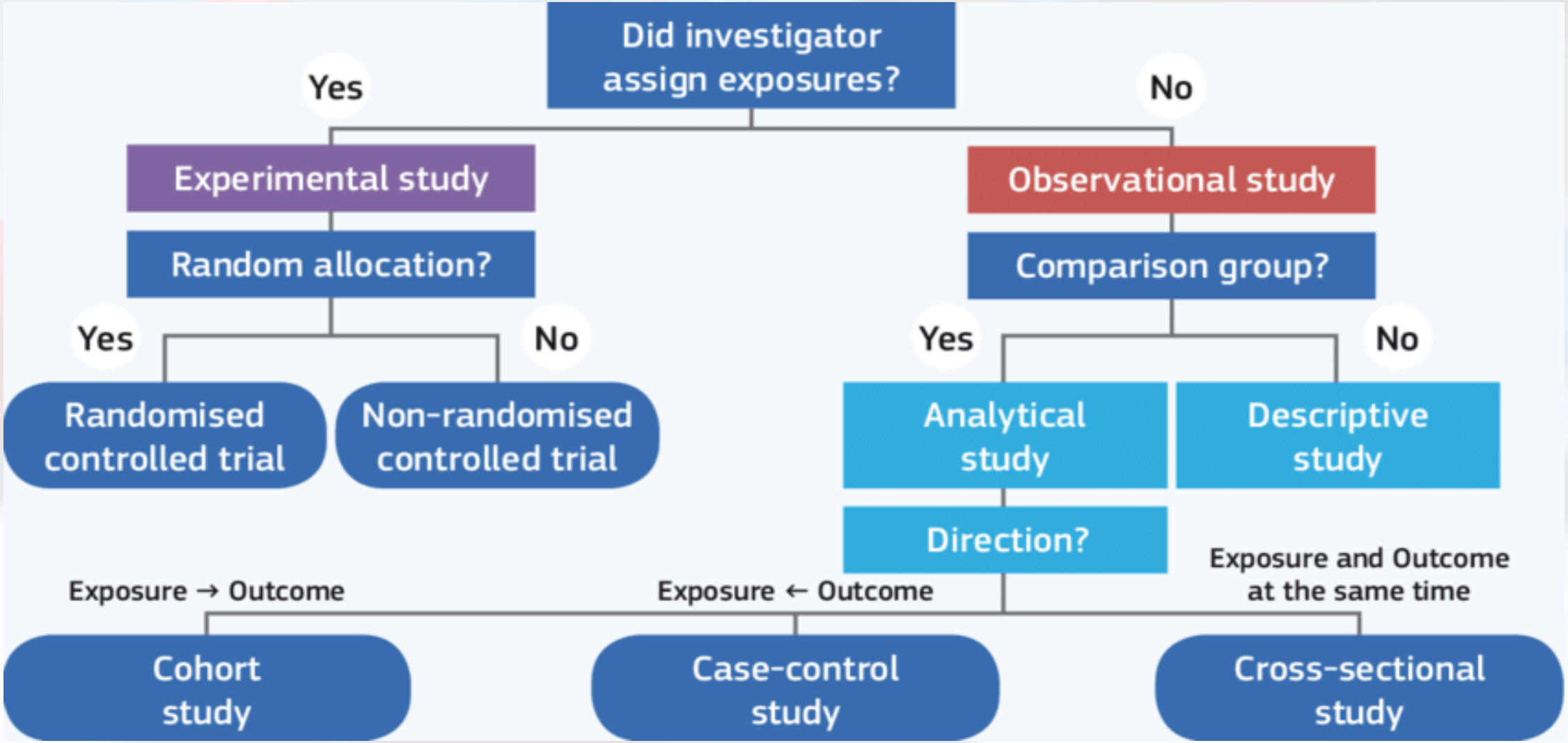
To highlight the landscape of clinical research, key considerations, the existing contentious issues, so as to guide strategies contextualized for implementing clinical studies in low resource settings .

Introduction to clinical research

Clinical research

- Can be biomedical or behavioral research studies involving human participants.
- **Clinical research has two large kingdoms:** experimental and observational research.
- The difference is in whether the investigators assigned the exposures e.g., treatments or device or whether they observed usual clinical practice.

Algorithm for classification of types of clinical research



Levels of research evidence

Level of evidence (LOE)	Description
Level I	Evidence from a **systematic review or meta-analysis** of all relevant RCTs (randomized controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from **at least one well-designed RCT** (e.g. large multi-site RCT).
Level III	Evidence obtained from **well-designed controlled trials without randomization** (i.e. quasi-experimental).
Level IV	Evidence from **well-designed case-control or cohort studies**.
Level V	Evidence from **systematic reviews of descriptive and qualitative studies (meta-synthesis).**
Level VI	Evidence from a **single descriptive or qualitative study**.
Level VII	Evidence from the **opinion of authorities and/or reports of expert committees.**

Source: Ackley, B. J., Swan, B. A., Ladwig, G., & Tucker, S. (2008). *Evidence-based nursing care guidelines: Medical-surgical interventions.* (p. 7). St. Louis, MO: Mosby Elsevier.

Overview on clinical trials (CTs)

- National institute of Health (NIH) Clinical trial definition (2014)/ WHO definition:
  - Any research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
- CTs may be referred to as interventional trials
- Interventions include but are not restricted to:
  - drugs, vaccines, cells and other biological products, surgical procedures, radiological procedures, devices, behavioural treatments, dietary choices and supplements, changes in lifestyles, process-of-care changes, preventive care, etc).

Randomized Clinical trials (RCT): Introduction

- It approximates the controlled experiment of basic science.
- The hallmark of RCTs is assignment of participants to exposures purely by the play of chance.
- RCTs reduce the likelihood of bias in determination of outcomes.
- When properly implemented, random allocation precludes selection bias.
- Could include blinding of those involved as to the exposure each participant is receiving thus reducing information bias.
- Eliminates confounding bias, both known and unknown.

Randomized Clinical trials (RCT): Draw backs

- **External validity issues:**
  - Whereas the RCT, if properly done, has internal validity (i.e., it measures what it sets out to measure) but might not have external validity.
    - This term indicates the extent to which results can be generalized to the broader community.
  - Unlike the observational study, the RCTs include only volunteers who pass through a screening process before inclusion.
    - Those who volunteer for trials tend to be different from those who do not; for example, their health might be better.
- **RCTs cannot be used in some instances,** since intentional exposure to harmful substances e.g. toxins, bacteria, or other noxious exposures would be unethical.
- **RCTs can be prohibitively expensive**.
- **RCTs may miss out on long-term effects** of the intervention.

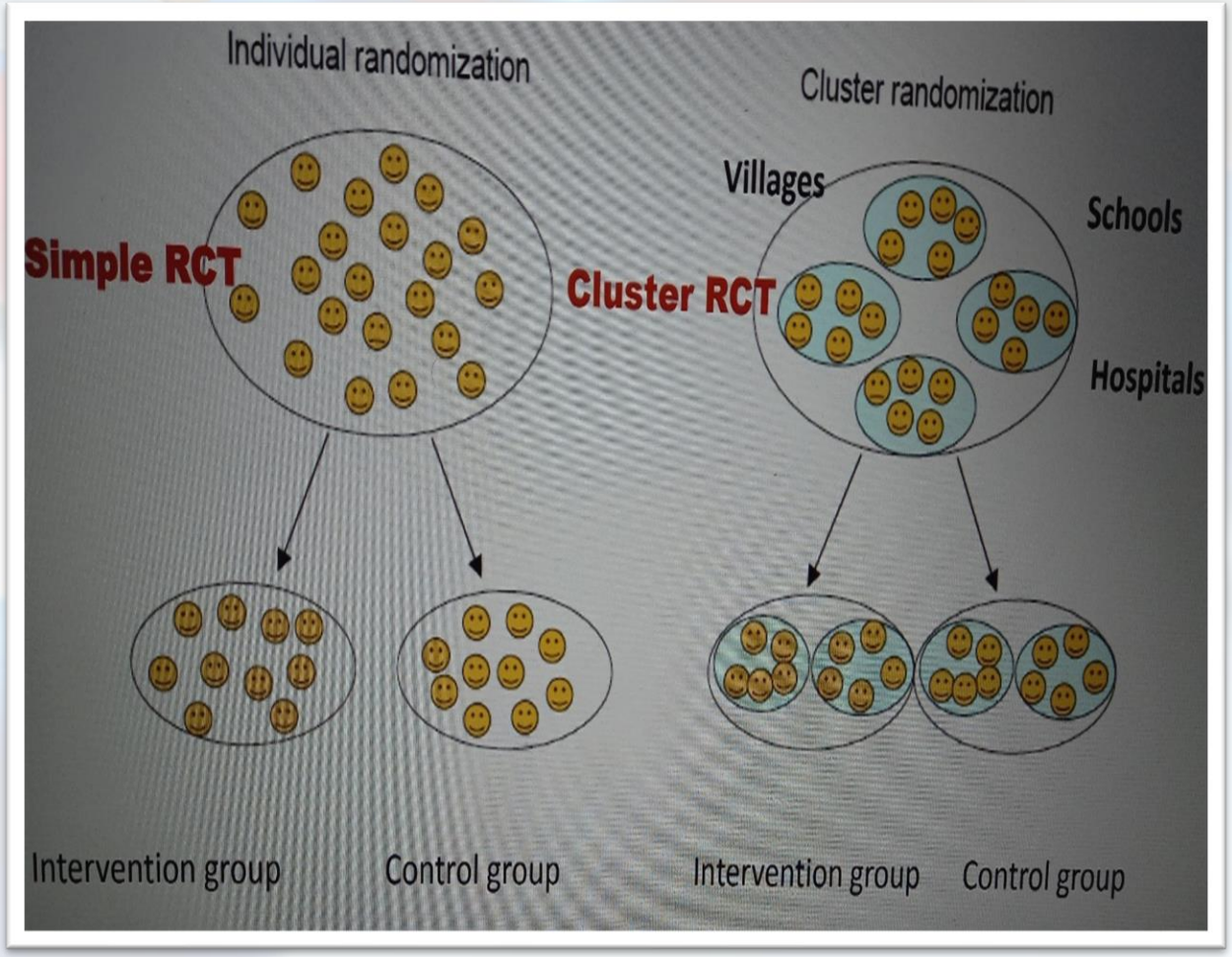
Classification of clinical trial in stages: *based on primary goals and number of participants*

Stage	Primary goal	No. of subjects
Preclinical	Analysis in non-human subjects, to preliminary evaluate efficacy, toxicity, and pharmacokinetics	-
Phase 0	Preliminary evaluation of efficacy, effectiveness and safety in healthy volunteers.	10-20
Phase I	Preliminary evaluation of efficacy, effectiveness and safety in healthy volunteers	20-100
Phase II	Evaluation of efficacy, effectiveness and safety in patients	100-300
Phase III	Evaluation of efficacy, effectiveness and safety in patients	>300
Phase IV	Post marketing surveillance	All subjects

Cluster randomized trials (CRTs): Introduction

- **Are clinical trials (Experiments) in which social units or clusters of individuals rather than independent individuals are randomly allocated to intervention groups.**
- All individuals within a given cluster are assigned to the same study arm.
- **Application:** in education and public health research
- **Well suited to testing differences in a method or approach to patient care** (as opposed to evaluating the physiological effects of a specific intervention)

RCT versus a CRT



Overview of conducting clinical research in low resource settings

- Conducting clinical trials in low-resource countries often presents significant:

  ethical, organizational, cultural, and infrastructural challenges to researchers, pharmaceutical companies, sponsors, and regulatory bodies.

- Globally, these regions are under-represented in research, yet this population stands to gain more from research in these settings
  - given their greater health burdens than those in resource-rich countries.
- Low-resource countries also offer an attractive setting for clinical trials because of:
  - a larger treatment naive population with higher incidence rates of disease and in more advanced stages.
  - Reduction in costs and time required to recruit patients.
  - Weak health systems making it easy to demonstrate impacts of new health care interventions
- A balance is needed with regard to the above benefits and vulnerabilities due to clinical research done in these settings.

Difficulties in implementing clinical trials in low-resource settings

- They rise from problems with:
  - recruitment, obtaining valid informed consent, ethical compensation mechanisms for extremely poor populations, retention, poor health infrastructure and considerable socioeconomic and cultural divides.
- Whether trials are investigator-initiated or driven by the pharmaceutical industry, the difficulties in their implementation in low resource settings tend to be crosscutting

Examples of difficulties in clinical research

1) **Absence of harmonized regulatory requirements and regulatory reliance**

2) **Administrative bottlenecks** especially in public institutions that lack research administrative bodies

3) **Financial bottlenecks**, especially when research budgets are not drawn after extensive ground work, thus resulting in under-budgeting

4) **Multiple languages and diverse cultures**, to be considered from the conception stages of research design and tools development

5) **Compensation mechanisms for research participants** varies between countries

6) **Interviewer compensation modalities:** should be discussed openly during the preliminary stages and contracts established

7) **Need for additional documents required to ease the collection of data:** to be identified and developed based on the realities of the context where the research is implemented

8) **Inadequate interviewer competence:** to be addressed through conscious budgeting and planning for training and capacity building

9) **Different ages for legal consent between countries:** necessitate country specific adaptations

10) **No dedicated research administrators in many settings.**

Researchers' recommendations towards implementation of high-quality clinical research in the low resource settings

1) **Training and capacity building for regulatory authorities** so as to harmonize research regulation standards

2) **Independent support networks for clinical trials** so as to ensure that specific challenges are addressed

3) **Channeling funds directly to the point of expenditure or development of efficient financial management systems for clinical research.** Sorts delays due to financial and administrative hurdles or bureaucracies

4) **Inclusion of local investigators at the conception and design stages** of a clinical trial may help to reduce the likelihood of unforeseen expenditures

5) **Financial audits** to ensure accountability

6) **Testing and verification of translations for accuracy.** Addreses possible language barriers

7) **Preparedness and adaptability** are essential ingredients for the successful conduct of clinical trials

8) **Establishing research administration infrastructure.** Allows the scientist to devote more time to the scientific aspects of the trial.

9) **Multisite trials should have national coordinators selected before the onset of the trial** to participate in conception.

10) **Investigator-initiated pragmatic trials** are arguably the way forward for clinical research in low resource countries and are usually needs-based and people centred.

11) **Comprehensive community engagement strategies** critical in planning trials to ensure that protocols are culturally sensitive, acceptable to the community and beneficial

12) **Trials to target the specific medical needs of the country as perceived by the country**.

13) **Recognition of the profession of Clinical Trial Scientist:** as a viable career path for researchers in low resource countries and training platforms should be set-up so as to raise such human resource capacity

Other contentious issues and considerations in the implementation of clinical research in low resource settings

Challenge in selection of study control groups for clinical trials in the context of outbreaks

- Selection of appropriate study control groups is vital in ensuring valid conclusions from clinical research.
- Methodological challenge: Difficulty in identifying the right control group in context of epidemics with rare diseases.
- For example, during the Ebola virus disease outbreaks in West Africa,
  - treatments with proven efficacy were needed. In as much as RCTs remain the gold standard for evaluating drug efficacy, they may be difficult to conduct due to ethical concerns and challenging field conditions in the context of disease outbreaks.
  - How can you administer nothing to a “control” Ebola patient since no other treatment options existed?

General participant recruitment issues

- **Inadequate strategies for timely participant recruitment** can increase the cost of clinical research if not given attention prior to implementation.

  strategies can vary according to study population, setting of the study, and disease under study.

Some recommended strategies:

- Using both retrospective and prospective methods. Could still be time-consuming in low-resource settings given the suboptimal medical records and difficulties in contacting historical patients.
- Trial budgets to cover sufficient pre-trial training for on-site researchers
- Consider in trial design: **use of phone and web-based electronic tools** to optimize recruitment and retention.
- Preliminarily ‘community sensitization’ procedures

Issues of willingness to participate in clinical trials

- Gender differences in willingness to participate (WTP) in clinical trials have been reported. For example, WTP was higher among women than men in a study evaluating different HIV prevention methods.
- Most influencing factors in trial participation are:
  - Social benefits (motivator)
  - Personal risks (most notably receiving injections and/or blood draws) were deterrents.
  - Potential participants' perceptions towards the effectiveness of the intervention being tested (could likely reduce WTP)

Contentious issues in enrolment and follow up of pregnant women in clinical trials

- Barriers have existed in obtaining data from pregnant/lactating women in clinical trials in an effort to protect them and their fetuses from research-related risks.
- Still various medications are used off-label during pregnancy/lactation despite a lack of data in this unique population and context.
    - Treatment and dosing strategies are based on standard adult doses even though dosing, safety and efficacy were determined in healthy and mostly male individuals.
- Trials in pregnant/lactating women are needed to inform their clinical care.
- Today, the story could be changing due to:
    - New published guidance to researchers and industry for recruiting pregnant women in drug development clinical trials. E.g US Food and Drug Administration (FDA)
    - Low resource countries normally adopt these guidelines

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Lack of harmonization on consent for children of minor parents participating in clinical trials

- Sub-Saharan Africa high rates of underage mothers
- Challenge exist in the right approach to consenting for clinical trial participation of infants with minor parents.
- Regulations are vague regarding the appropriate decision-maker and authority to consent for children of minor parents participating in clinical trials.
- **This lack of guidance may affect:** 1) the rights of potential pediatric participants already bearing increased vulnerability. 2) recruitment and generalizability of the research.
- **Diversity of options in informed consent (IC) approaches;**
  - Individual consent by minor parents based on emancipation or “mature minor” status.
  - Basing consent on guidance of national laws on medical care.
  - When no laws or guidance existed an interpretation of the local decision-making culture, including community engagement and collaboration with local ethics committees, defined the informed consent approach.
  - Implementation of informed consent for children with minor parents may be:
    - variable and hampered by absent or ambiguous clinical trial regulations, as well as divergent local realities.
    - be influenced by the research area and study-specific risks.

Participants loss to follow-up or retention

- **Sample size and retention of the required number of subjects at the completion of the follow-up period are crucial factors in the ability of RCTs to provide credible and generalizable data.**
- **Loss to follow-up poses a major problem for researchers in different ways:** 1) Risks reduction in the power of the study. 2) Risks biases in case it occurs in a specific group of patients, hence impact on the validity and generalizability of the study results.
- **Reason for trial non-completeness**
  - Consent withdrawal: main in some children trials, due to father non engagement at consent and parents being comfortable with blood sampling.
  - Participants thinking that they did not need frequent visits
  - Time constraints
  - Migration for better employment
  - Travel distance to the trial site

- **Potential solutions to retention enhancement:**
  - Involvement of fathers at consenting.
  - Continuous community involvement in the process
  - Restriction in eligibility criteria eg no prisoners
  - Use of treatment supporters
  - Adequate explanation of trial procedures and risks/benefits
  - Innovative tracing of participants adapted for the setting
  - Good participant and research team relationship
  - Continuous counselling and support to patient
  - Logistical support to patients eg Time compensation and transport re-imbursement
  - Limiting radius of the participant catchment area
  - Home-based or community-based patient follow-up
  - phone call follow-up e.g during COVID-19 restrictions
  - wide stakeholder engagement
  - Develop a participant retention plan

Shortfalls and recommendations in the strategies used to elicit adverse effects data from participants in clinical trials.

- Analysis of drug safety in clinical trials involves assessing Adverse Events (AEs)
- **Methods of ascertaining AEs:** 1) Physical examinations or tests, 2) Great reliance on reports from participants to detect subjective symptoms, where he/she is often the only source of information. (questioning method)
- No consensus on how these reports should be elicited although it is known that questioning methods influence the extent and nature of data detected. This leaves room for measurement error and undermines comparisons between studies and pooled analyses.
- **More specific questioning of participants (checklist-based) lead to more AEs detected compared to a more general enquiry.**

Challenges in conducting trials in Children

- RCTs in children are uncommon in low resource settings.
- Challenges can be cross-cutting across trials and can be related to:
  - Diagnosis
  - Management of sick children
  - Large catchment areas
  - Adverse event attribution
  - Concomitant medications
  - Infrastructure requirements
  - Expensive pediatric formulations with short expiry
  - Detection of treatment response in a highly variable disease across the age continuum.
  - Need for extensive and specialized training and adaptation of tools were necessary.
  - Special care to explain study participation to distressed caregivers and manage children longitudinally.
- Overall, trials in pediatric populations in low resource settings may be challenging but are critically important for improving the treatment of a pediatric diseases and their outcomes.

Community involvement in research in resource limited settings

- Researchers must consciously build partnerships with and learn about the community's social and cultural perspectives.
- **Community engagement activities facilitate:** preventing public mistrust, increasing acceptance, adoption and participation in the trial.
- **Community-engaging research involves:** protecting individuals from research risks, as well as considering community-level concerns.

Major goals of community engagement are:

1. To build transparent, meaningful, collaborative, and mutually beneficial relationships with interested or affected individuals, groups of individuals, or organizations, which shape research collectively
2. To ensure that research is responsive to the needs, priorities and expectations of the communities involved in research and or being researched on
3. To ensure the relevance of the proposed research to the affected community and its acceptance and ownership by the community
4. Building, strengthening, and sustaining trust between researchers and communities.

Community advisory boards (CABs)

- A functional Community advisory board (CAB) is a key requirement by research regulatory bodies.
- CABs influenced the informed consent process for clinical trials or other aspects of research ethics.
- **CAB responsibilities include:** reviewing study protocols, educating local communities about research activities, and promoting the ethical conduct of research.
- **Challenges faced by CABs**:
  - Incomplete ethical regulations and guidance
  - Limited knowledge of science among members of communities and CABs
  - Unstable and unbalanced power relationships between researchers and local communities
  - Poor CAB management, including lack of formal participation structures and absence of CAB leadership
  - Competing demands for the time that limited participation in CAB activities
  - Language barriers between research staff and community members.
- **Solutions:**
  - Ethics training needed among CAB members and researchers in LMICs.
  - Developing national guidance on community engagement structures

Maintaining data integrity in a rural clinical trial in low resource settings

- Obtaining and maintaining data integrity in rural clinical trials is feasible, can result in acceptable data quality and can be used to develop capacity in developing country sites.
- Challenges in ensuring the quality of data collection and handling.
- Initial difficulties:
  - The unavailability of experienced and skilled human resource e.g. research nurses, programmers and data managers in many remote settings
  - Difficulty of designing new software tools and a complex database while making them error-free.
- **Mitigation measures:**
  - Initial and refresher training for research team
  - National and international collaboration and external monitoring help in: ensuring good data handling and implementation of good clinical practice
  - Streamlined transport means to support data collection, fieldwork supervision and query handling
  - Involvement of a CAB in addressing cultural issues and establishing community acceptability of data collection methods.

Minimizing patients' ineligibility to trials

- **Patient ineligibility to trials can be a major cause of:**
  - delay in the trial recruitment process
  - big financial investment in screening but with supoptimal gains.
- **Key reasons for ineligibility in RCTs:**
  1) Use of nonindigenous laboratory references (major reason)
  2) Medical abnormalities
  3) Declined enrollment. In a nutshell, it is essential that
- **Use of laboratory reference ranges generated from local populations for laboratory values can avoid:**
  - Unnecessary exclusion of willing participants
  - Over-reporting of adverse events for enrolled participants

Regulatory landscape for clinical research utilizing biomedical devices in Africa

- Access to medical devices and in vitro diagnostics is often limited in Africa necessitating innovation and research.
- The **regulatory frameworks for pharmaceutical products are quite advanced** but the pathway for other health products including medical devices has received less attention in most African countries
- **Guidance on use of medical devices in most African countries is still scanty** despite the rapidly evolving scope and sophistication of medical devices is.
- The National Guidelines for Research Involving Human Subjects (2014) by the Uganda National Council for Science and Technology refer to the National Drug Authority (NDA) for any research involving drugs and devices.
- **The current scope of regulation of medical devices in Uganda** is limited to the importation, manufacture, export and supply of medical devices.

Regulatory landscape for clinical research utilizing biomedical devices in Africa

- **The Uganda National Drug Authority (NDA) guidelines on medical devices are limited to:** registration of surgical instruments and appliances as well as Quality requirements for medical face masks and do not extend to the conduct of research.
- **NDA guidelines for the conduct of clinical trials in Uganda (2019) provide for** submission of a clinical trial application for studies using a medical device to deliver a drug or medicinal product to a human participant.
- All other uses of medical devices beyond this scope do not require regulatory review and approval by the NDA under the current framework.
- **The vacuum in clear regulatory frameworks for the conduct of biomedical research involving medical devices as well as the paucity of device-related clinical trials** demonstrates a significant gap in locally generated data that informs the registration/market authorization of these devices.

Challenges in recruiting community controls

- In hospital-based case-control studies, population controls can help ensure generalizability, but their selection can be challenging in environments that lack population registries.
- **Some of the innovative strategies that have been tested in some studies include:**
  - **population enumeration based on census data**. In this method, census defined geographic areas are identified and a household enumeration is done so as to generate a sampling frame and potential participants selected using systematic random sampling and frequency-matched to the anticipated distributions of age and residence among cases. These can then be contacted, assessed for eligibility and consented to participate in the study as controls.
- **Common reported reasons for non-participation by population controls:** 1) lack of interest, 2) lack of time.
- **Some innovative strategies to ensure a good response rate or participation rate include:**
  1. **Multiple attempts to contact potential controls** to assess eligibility and arrange for study participation.
  2. **Implementation of a refusal conversion protocol** in which initial non-participants are re-approached after several months. This approach could guide researchers undertaking epidemiologic studies in populations that lack accessible population registries.

Ethical challenges in cluster randomized controlled trials

- Public health interventions usually operate at the level of groups rather than individuals, and cluster RCTs are one means of evaluating their effectiveness.

1) Nature of – and responsibility for – group consent
2) Need for consent by individuals within groups to intervention and data collection
3) Timing of consent in relation to the implementation of public health strategies
4) The problem of securing ethical review and approval in a complex domains
5) Benefits to control groups and the standard of care that they should receive
6) The issue of post-trial adoption of the intervention under test.`

1. Nature of – and responsibility for – group consent in Cluster randomized trials (CRTs)

- CRTs involve two levels of consent: for the involvement of the group and the individual.
- Group consent is challenging.
- Common cluster guardians: local guardians or representatives (e.g. elected leaders, community elders or group heads)
- In communities, in which collective decision-making is customary, communal leaders may express the collective will.
    - Could be contested given that communities are usually a mixture of smaller communities
    - In a complex society, how do we identify individuals – or groups – who speak for the many?

2. The need for consent by individuals within groups to intervention and data collection

- Group consent is not a substitute for individual consent.
- Individual informed consent should be sought and well documented.
- Community members should be made aware of the trial and asked if they would like to participate.
- An individual's right to refuse to participate should be respected, despite consent at the representative level
- Trial documentation should clarify the opportunities for cluster members to avoid the risks associated with an intervention.

Some approaches to cluster/group consenting

- Document the choice of community representatives and reasons for approaching them.
- Make the process of cluster consent as open as possible.
- One type of person can represent a community, so seek agreement from a range of stakeholders.
  - Have them sign different consents or seek their written support for the research project.
- Community/consultative meetings: to sensitize on clinical trial and seek consent
  - Increases inclusiveness in the decision to allow a clinical trial.
- Rely on national guidelines for community engagement
- In some settings, fall back on permission from political and cultural leaders, elected members and community organizations.
- Do individual consenting instead of Cluster guardianship:
  - especially when individuals are able to decide for themselves whether to be physically involved in the trial.

3.Timing of consent in relation to the implementation of public health strategies or interventions

- Consent after randomization is common in cluster RCTs.
- In CRTs common procedure is:
  - Choose a population, define and draw a random sample of clusters in which the trial will be done, randomize the allocation, then seek consent from cluster members.
- In an individual-based RCTs:
  - Consent is obtained for participation and then the randomization process is explained so that the participant is aware that she/he may or may not receive the intervention under test.
- Presumably a similar approach should apply to clusters:
  - Seek cluster members' consent for inclusion in the trial, and explain that data collection will be done across all study clusters, but that allocation of intervention will be random.
- It is undoubtedly true that some representatives of control areas may not be happy that they would not receive the intervention under test until a later date

4. The problem of securing ethical review and approval in a complex domain

Two particular challenges to ethical review are common in low resource settings.

1. Finding a research ethical committee with capacity to review an RCT in some settings.
2. Lack the capacity to ably review certain projects despite existence of REC in some settings:
    - Due to an ever-evolving complexity in research (research methods, designs and research areas)

Potential solutions:

- Seeking external expert reviewers__Causes delays in the approval process.
- Continuous capacity building for RECs
- Pre-submission or intra-review presentations of complex RCTs by principal investigators.

5. Benefits those participants in control groups and in the standard of care should receive

- Because public health interventions are usually not masked, the possibility of “resentful demoralization” in members of control groups is high.
- Public health interventions may be conceptually different if the aim is to improve the general quality and uptake of care **in a situation of vulnerability, limited resources, inequity and system weaknesses.**
- The general belief is that control groups should receive benefits for participation, although the scope of reasonable benefits is uncertain.
- **Key considerations:**
  - Provision of care to controls that is not directly linked to the research question (ancillary care)
    - Ongoing debate among research regulators in low resource settings.
    - “no survey without service”: a common ideology among researchers
    - A duty of care for people in control clusters when data collection teams identify health risks.
    - Researchers are happy to break protocol if individuals are at risk, assisting them, for example, with transport and negotiations for emergency medical care and later document and report protocol deviations.

6. The issue of post-trial adoption of the intervention under test

- A CRT is the first step in the roll-out of an intervention that may benefit public health.
  - Successful intervention should be rolled out to the control groups, with modifications based on experience.
  - Participants in a CT should have the opportunity to access superior care if the trial shows that one intervention is more effective than another, and communities involved in studies should benefit in the long run.
- Guidance on post-trial access is still low in Africa.
- For consideration by researchers, sponsors and funders at conception and budgeting of a research project.
- **Setbacks or challenges towards implementing post-trial adoption of interventions under test in a CRT.**
  1. The CRT is less of a gold standard than it might appear, and often require replication in different contexts to deal with questions about generalizability or simply to develop a groundswell of conviction.
  2. Research funding bodies are generally not in the business of roll-out.
     - The onus on researchers to try to leverage uptake by (usually) the public sector.
       - Beyond notional agreement, the commitment of resources may still be a problem.
     - Involving many partners in identifying, developing, conducting and disseminating research is one way to leverage such commitment.

Conclusion

- Low-resource settings offer a good environment for clinical research given there high burden of disease.
- However, measures to mitigate the anticipated challenges in research implementation that could differ across countries.
- Efforts towards fast-tracking harmonization in research conduct and monitoring of the changing landscape remains useful
  - Could guide researchers, regulators, sponsors and funders involved in research within low resource settings.
- Knowing the discussed challenges could support adequate planning of clinical research in low resource settings.

Soar Research Foundation
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You are welcome to implementing Clinical research in Africa

Thank You

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