STANDARDS FOR RESEARCH IN (StaR) CHILD HEALTH

There are special considerations for undertaking health research with children. These include the ethical obligation to optimize the value of their participation and to safeguard them from avoidable harms.

In 2012, Standards for Research in (StaR) Child Health published Standards to guide the rigorous design, conduct, and reporting of child health research in six priority areas:

SIX PRIORITY AREAS

Consent and recruitment
Well-designed consent procedures are essential to ethically sound recruitment

Containing risk of bias
Biases can lead harmful or ineffective treatments to be prescribed or effective ones to be withheld

Appropriate age groups
Trials should account for age differences and consistently report age-related data to ensure valid, useful results

Selection, measurement, and reporting of outcomes
Outcomes should be relevant to all stakeholders, including children and families

Determining adequate sample sizes
The sample size calculation is a matter of Good Clinical Practice when designing a trial

Data monitoring committees (DMCs)
A DMC protects the safety of participants and the ability of the trial to yield reliable results

These summaries provide the key design, conduct, and reporting considerations related to each of the six priority areas. They are designed to complement the detailed guidance within each published Standard.

Trainees, clinicians, and researchers may find these summaries useful to learn about and guide the design, conduct, and reporting of child health research.

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CONSENT & RECRUITMENT

Well-designed consent procedures are essential to ethically sound recruitment

RESPECT CONSENT AND ASSENT

Obtain consent from parents or caregivers, and assent from children

Discriminate between true dissent, and age-appropriate reactions from children

TAILOR YOUR MATERIALS

Information about your trial should be brief, age appropriate, and easy-to-read

SELECT PARTICIPANTS FAIRLY

All eligible children should have an equal opportunity to take part in your trial

KEEP PARTICIPANTS INFORMED

Children and families need information about your trial, but too much information is overwhelming

Children and their families need to know:

- What your trial entails
- The time commitment required
- Potential benefits, discomforts, and risks
- If they will be compensated
- Their rights and compensation if harmed
- Their right to refuse participation or to withdraw
- Alternative treatments
- Any conflicts of interest
- Who to contact with questions or concerns

BE CLEAR ABOUT YOUR ROLE

Children and families need to know which procedures are part of usual care, and which are part of your trial

ASSESS THE BENEFITS AND RISKS

Share known benefits and risks with children and families

Children living in institutions and low-resource settings are particularly vulnerable

WEIGH THE PROS AND CONS OF INCENTIVES

Incentives and payments can enhance recruitment, but can compromise voluntariness

Incentives and payments are acceptable unless they lead participants to ignore, misunderstand, or undervalue the risks of participating

For more information, see: Caldwell PH, Dans L, de Vries MC, et al. Standard 1: consent and recruitment. Pediatrics. 2012;129 Suppl 3:S118-23.

CONTAINING RISK OF BIAS

Biases can lead harmful or ineffective treatments to be prescribed or effective ones to be withheld

REGISTER YOUR TRIAL AND WRITE A PROTOCOL

Trials can be registered in any registry that is a primary register for the *World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)* or at *ClinicalTrials.gov*

RANDOMIZE PARTICIPANTS TO INTERVENTION GROUPS

Randomization creates groups that are balanced with respect to confounders and reduces the risk of selection bias

Appropriate randomization methods include:

- Computerized random numbers generators
- Simple methods like picking a number from a hat

Avoid non-random methods like:

- Time of day
- Day of the week
- Odd and even numbers

ACKNOWLEDGE YOUR FUNDERS AND THEIR ROLE

Influence tied to support received may introduce biases and conflicts of interest

CONCEAL THE RANDOMIZATION SEQUENCE

Concealing the randomization sequence from participants, their families, or trial personnel until group assignment reduces the risk of selection bias

Appropriate concealment methods include:

- Opaque, sealed envelopes
- Identical drug containers
- Centralized allocation (e.g., pharmacy)

REPORT ON ALL OUTCOMES

Reporting all outcomes (positive, negative, or null) minimizes the risk of reporting bias

Report any changes in outcomes or the way they were measured and analyzed compared to the protocol

TRACK YOUR PARTICIPANTS

Keeping a record of how many children withdrew or were lost to follow up will help to detect attrition bias

Collecting detailed contact information can help reduce losses to follow up

BLIND PARTICIPANTS AND PERSONNEL FROM GROUP ASSIGNMENTS

Blinding group assignment from participants, their families, and trial personnel reduces the risk of performance and detection bias

For more information, see: Hartling L, Hamm M, Klassen T, et al. Standard 2: containing risk of bias. Pediatrics. 2012;129 Suppl 3:S124-31.

AGE GROUPS

Trial designs that account for age differences and promote consistency in the reporting of age-related data are essential to ensure valid and clinically useful results

CONSIDER INTEGRATED AGE GROUPS

The *Eunice Kennedy Shriver National Institute of Child Health and Human Development* (NICHD) has defined age stages that may be used to establish age groups and age-based sub-groups for child health trials

AGE STAGES DEFINED BY NICHD PEDIATRIC TERMINOLOGY

Stage	Definitions
Preterm neonatal	The period at birth when a newborn is born before the full gestational period
Term neonatal	Birth to 27 days
Infancy	28 days to 12 months
Toddler	13 months to 2 years
Early childhood	2 to 5 years
Middle childhood	6 to 11 years
Early adolescence	12 to 18 years
Late adolescence	19 to 21 years

PLAN AHEAD

Decide on eligible age groups, age-related stratification, and subgroup analyses ahead of the trial

JUSTIFY THE SELECTED AGE GROUP IN THE FINAL REPORT

Describe in detail:

- Whether age groups were decided a priori
- How and why the age groups were selected
- The method used to ascertain participants' ages

CHOOSE AGE-APPROPRIATE OUTCOMES

Not all outcomes will be relevant or appropriate for children of all ages

Outcomes are sometimes measured differently in children of different ages

For more information, see: Williams K, Thomson D, Seto I, et al. Standard 6: age groups for pediatric trials. Pediatrics. 2012;129 Suppl 3:S153-60.

SELECTION, MEASUREMENT, AND REPORTING OF OUTCOMES

Trials should measure outcomes that are relevant to all potential stakeholders, including children, their families, regulatory authorities, funders, and policymakers

ADOPT A CORE OUTCOME SET IF AVAILABLE

Core outcome sets are a minimum set of outcomes that should be measured for a given condition in a standardized way

The COMET initiative aims to facilitate the development and application of core outcome sets

SELECT IMPORTANT OUTCOMES

Select outcomes that are important to all stakeholders and relevant to clinical decision-making

MEASURE OUTCOMES RIGOROUSLY

Use measures that are valid in the age group under study, with the condition of interest, in the setting that the trial is conducted

Measures must be responsive, and sensitive enough to reliably detect clinically important differences

Consider conducting validation studies if existing measures have not been validated

REPORT OUTCOMES AND MEASURES FULLY

Be completely transparent as to:

- Planned outcomes and how they were decided
- Who measured and reported the outcomes
- The measures used to assess the outcomes
- When the outcomes were measured
- Definitions of event endpoints
- Previous validation work

Report any changes to the outcomes and how they were measured compared to the protocol

For more information, see: Sinha IP, Altman DG, Beresford MW, et al. Standard 5: selection, measurement, and reporting of outcomes in clinical trials in children. Pediatrics. 2012;129 Suppl 3:S146-52.

DETERMINING ADEQUATE SAMPLE SIZES

Recruiting too many children risks unnecessary exposure to potentially inferior treatments, whereas recruiting too few will lead to inconclusive or unreliable results

CONSULT A STATISTICIAN OR METHODOLOGIST WHEN PLANNING YOUR TRIAL

A statistician or methodologist has the expertise to calculate an appropriate sample size

A statistician or methodologist can help overcome issues related to feasibility and resource or timeline constraints

CALCULATE THE SAMPLE SIZE NEEDED FOR YOUR TRIAL

Standard procedures should be used when information from previous studies is available

You will need:

- The control event rate (for dichotomous outcomes)
- The minimum clinically important difference (MCID), or expected treatment event rate
- The MCID between mean outcomes
- The type I error rate (α) (probability of false positives)
- The statistical power (1-ß)
- The standard deviation (for continuous outcomes)

CONSIDER ALTERNATE SOURCES OF DATA

Trials that evaluate similar treatments or use other designs may be suitable when research specific to your population is not available

If no reliable information exists, consider:

- Conducting an internal pilot study following an estimated sample size from adult trials
- Assuming a moderate treatment effect

REPORT ON THE SAMPLE SIZE CALCULATION

Report the calculated sample size and the parameters used for the calculation

EMPLOY GOOD FOLLOW UP PROCEDURES

Good follow-up procedures are essential to minimize losses to follow up

Effective strategies may include:

- Reminder e-mails
- Letters and self addressed stamped envelopes
- Monetary incentives
- Offering donations to charity
- Entry to a prize draw
- Telephone follow up

CONSIDER OTHER STUDY DESIGNS

If the number of available participants will be limited but a large sample size is needed, or if funding, feasibility or timeline constraints exist, alternative trial designs may be an appropriate solution

A statistician can help deciding on appropriate alternative designs

Options include:

- A crossover trial
- Repeated measures
- Meta-analyzing N-of-1 trials
- An adaptive design (e.g., sequential or internal pilot design)
- Collaborating on a prospective meta-analysis

For more information, see: van der Tweel I, Askie L, Vandermeer B, et al. Standard 4: determining adequate sample sizes. Pediatrics. 2012;129 Suppl 3:S138-45.

DATA MONITORING COMMITTEES (DMCs)

A DMC protects the safety of participants and the ability of the trial to yield reliable results

CONSIDER IF YOUR TRIAL NEEDS A DMC

In some trials, the monitoring of conduct, accruing results, and safety data should be undertaken by an independent panel of experts

You will need a DMC if:

- You are investigating a new intervention
- Few safety data are presently available
- Your trial addresses major morbidity or mortality endpoints
- The participating population is high risk
- You have planned interim analyses
- There is a possibility of early stopping
- Your sample size is large
- Your trial will be undertaken at multiple centers

IF YOUR TRIAL NEEDS A DMC, YOU SHOULD: KEEP THE DMC SMALL

The DMC should include one or more relevant clinician experts and a statistician or clinical trial methodologist

A consumer/community advocate (often a parent) may also provide a helpful perspective

Report unavoidable conflicts of interest

IF YOUR TRIAL NEEDS A DMC, YOU SHOULD: DEFINE THE DMC'S RESPONSIBILITIES

The DMC should regularly review trial data and develop recommendations for trial modification and continuation

Broader responsibilities may include:

- Reviewing and approving the trial protocol
- Releasing interim data
- Reviewing and approving manuscripts and presentations

IF YOUR TRIAL NEEDS A DMC, YOU SHOULD: REPORT ON THE DMC'S ACTIVITIES

Reporting the DMC's activities allows readers to evaluate their impact on the validity of trial results

Reports must include the DMC roles, results of interim analyses, and if early termination occurred

IF YOUR TRIAL NEEDS A DMC, YOU SHOULD: OUTLINE THE DMC'S ROLES

The DMC should be governed by a DMC charter that outlines their roles and responsibilities

The charter is prepared by the sponsor and approved by the DMC before their review of any interim data

For more information, see: Ellenberg S, Fernandes RM, Saloojee H, et al. Standard 3: data monitoring committees. Pediatrics. 2012;129 Suppl 3:S132-7.

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