Additional Safeguards for Children in Research and Protocol Review Under 21 CFR 50.54

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Topics Covered

- Additional Safeguards for Children (21 CFR 50 subpart D)
- Component Analysis
- 21 CFR 50.54 Protocol Referral
- Alternative Venous Access Methods
- Applying Component Analysis
- Questions for the Committee

General Justification of Research Risk (Adult and Pediatric)

- Criterion for IRB approval of research
  - Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result
    - *21 CFR 56.111(a)(2)*

- This criterion is modified by the additional protections for children enrolled in FDA-regulated clinical investigations in that there is a limit to the risk that knowledge can justify

Additional Safeguards for Children 21 CFR 50 subpart D

- Criterion for IRB approval of research in children
  - No more than minimal risk (§50.51) or
  - Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (§50.52) or
    - present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives
  - Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about subjects' disorder or condition (§50.53)
    - No more than a "minor increase over minimal risk"
    - Intervention or procedure is reasonably commensurate with expected medical situations
    - is likely to yield vital important generalizable knowledge about the subjects' disorder or condition
- Permission by parents or guardians and for assent by children must be solicited (§50.55)

Additional Safeguards for Children
21 CFR 50 subpart D

- Research not approvable under 21 CFR 50.51/ 50.52/50.53 may be approved under 21 CFR 50.54
  - If an IRB has determined that the research offers a reasonable opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children and
  - The Commissioner of the FDA after review by a panel of experts and a period of public comment determines that
    - The protocol does not meet requirements under 21 CFR 50.51/50.52/50.53
    - The protocol may be allowed to proceed, as long as the investigation is conducted using sound ethical principles and adequate provisions are made to obtain the permission of the parents and assent of the child (21 CFR 50.55)

Prospect of Direct Benefit (PDB)

- A “direct benefit” may improve the health or well-being of the individual child and results from the research intervention being studied (and not from other clinical interventions included in protocol).
- What evidence (e.g., from adult humans or animal disease models) is available about this intervention/product?
  - Do these data make us reasonably comfortable that children might benefit from this intervention/product?
  - Is the dose and duration of treatment with the investigational drug long enough to offer the intended benefit?
  - For diagnostic procedures, would the procedure normally be done as part of routine clinical care? Would the data potentially impact on clinical care?

Minor Increase over Minimal Risk†

- “Minimal risk” was originally defined as those risks “normally encountered in the daily lives, or in the routine medical or psychological examination, of healthy children.”
- "Minor increase" refers to a risk which, while it goes beyond the narrow boundaries of minimal risk…, poses no significant threat to the child's health or well-being.”
- “Given this conservative limit, the… promise of [substantial future benefits to children other than the subject] does justify research which goes beyond, but only slightly beyond, minimal risk.”
- Interventions/procedures that do not present a prospect of direct benefit must present no more than a minor increase over minimal risk, and be limited to children with a “disorder or condition” (absent federal review and approval).

† National Commission - Report on Research Involving Children (1977)

Component Analysis

- A clinical investigation may include more than one intervention or procedure.
- Each intervention/procedure must be evaluated separately to determine whether it does/does not hold out the prospect of direct benefit to the enrolled child.
  - This approach is consistent with recommendations of the National Commission and the resulting regulations.
- Interventions or procedures that hold out the prospect of direct benefit should† be considered under 21 CFR 50.52.
- Interventions or procedures that do not hold out the prospect of direct benefit should † be considered under 21 CFR 50.51 or 50.53 (but not 50.52).

† Can be considered under 21 CFR 50.54 (thus "should" and not "must")

Component Analysis

- Failure to carefully distinguish the different components of a clinical investigation may result in the risks of an intervention or procedure that does not hold out the prospect of direct benefit exceeding the allowable ceiling of a minor increase over minimal risk (absent referral under 21 CFR 50.54).

Referral of ESSENCE for Review Under 21 CFR 50.54

- ESSENCE is a double-blind, multi-center, placebo-controlled, 96-week study to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in Duchenne Muscular Dystrophy (DMD) patients with genotypically confirmed deletion mutations that are amenable to skipping exons 45 or 53.
- Boys with DMD, an X-linked chromosome disorder, have a gene defect that results in decreased production of dystrophin, a muscle sarcolemma protein. Without dystrophin, the muscle membrane is destabilized resulting in the muscle weakness, motor delay and associated symptoms characteristic of the disease.
- SRP-4045 and SRP-4053 are phosphorodiamidate morpholino oligomers (PMO) or synthetic versions of naturally occurring nucleic acids designed to bind to targeted pre-mRNA sequences, causing the areas of exon deletion in the gene to be skipped and allowing further production of a potentially functional modified dystrophin by restoring the reading frame.

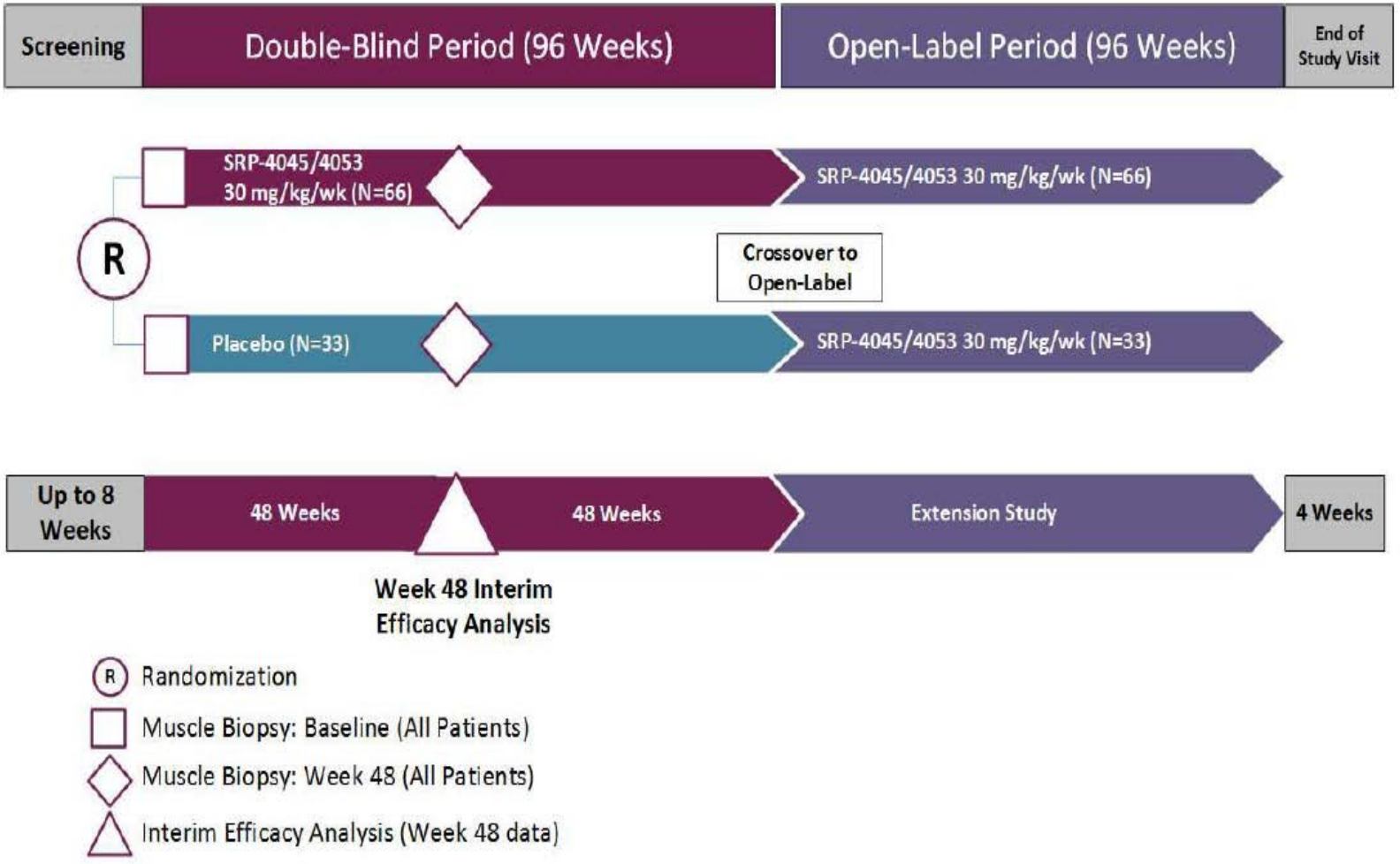
Referral of ESSENCE for Review Under 21 CFR 50.54

- In 2015, ESSENCE was reviewed by FDA
- At that time, the study specified that a venous access port could be used at the discretion of the investigator; other venous access methods were not specified.
- FDA informed the sponsor that implantation of a venous access port for patients in the placebo arm of the study exceeded a minor increase over minimal risk and offered no prospect of direct benefit, and consequently was not approvable under 21 CFR 50.51, 50.52 or 50.53.
- The sponsor subsequently amended the protocol to preclude the use of a port at sites in the United States.

Referral of ESSENCE for Review Under 21 CFR 50.54

- In March 2017, the UCLA IRB received a “complaint” from a parent with a child with difficulty with intravenous access, asking why the use of indwelling infusion ports was not allowed in the protocol.
- Consequently, the IRB reviewed the protocol and was “unanimous in finding that the clinical investigation (including potential use of central venous catheters) represents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children.”
- An amended version of the protocol with an option to allow use of alternative venous access methods, including midline catheters, central lines and ports at all study sites was referred to the FDA for review under 21 CFR 50.54.

ESSENCE Protocol



Use of Alternative Venous Access Methods

- Problems with venous access may occur in patients with DMD due to contractures, positioning issues, fragile veins due to steroid use and scarring.
- In Sarepta's DMD clinical trial experience to date with multiple products, over half the study participants (52%, N=56) have had a port placed for infusions, with approximately 40% (N=21) placed due to loss of peripheral IV access during the course of the study. In one study, 8 of 12 patients required port placement between weeks 68 to 183 with a mean of 109 weeks.
- Techniques to aid in peripheral intravenous (PIV) insertion such as infrared visualization have varying rates of success in non-DMD patient populations.

Use of Alternative Venous Access Methods*

Access Option	Advantages	Disadvantages
Midline Catheter (MC)	-Lowest complication rate, infection rate similar to PIV -General anesthesia is not required	-Limited lifespan on the order of days to weeks -Harder to manage in pediatric patients than implanted port
Peripherally Inserted Central Catheter (PICC)	-Can be used for weeks to months -General anesthesia may not be required but IV sedation may be required for younger patients	-Shorter lifespan than implanted port -Higher complication rate (infection/occlusion) than implanted port or MC -Harder to manage in pediatric patients than implanted port
Central Venous Catheter (CVC)	-Tunneled CVC may be in place for years, non-tunneled for days -General anesthesia may not be required	-Difficult to perform in pediatric patients due to catheter size and vessel diameter Higher complication rate (infection/occlusion) than PICC, implanted port or MC -Harder to manage in pediatric patients than port
Venous Access Port (Portacath)	-Port life estimated to be 2 to 6 years -Lower complication rate (infection/occlusion/breakage) and replacement rate compared to PICC or CVC	-General anesthesia is required -More invasive than other options

*Information taken from the Meeting Background Document

Non-therapeutic Procedural Sedation

- The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met in in March 2015 to discuss the use of procedural sedation for non-therapeutic research interventions
- The PES/PAC was unable to reach consensus on whether one or more approaches to procedural sedation should be considered a minor increase over minimal risk (YES: 7; NO 9).
- The committee did agree upon recommendations that should be included in a protocol to consider if the protocol is approvable under 21 CFR 50.53 or if review under 21 CFR 50.54 is required.†

†http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM510177.pdf.

Applying Component Analysis to ESSENCE

- Patients who receive active treatment with SRP-4045 and SRP-4053 directly benefit from participation in the study.
- Risks of MC, PICC, CVC or portacaths needed to administer the active treatment are judged against the potential benefits of the drug.
  - Risks of non-therapeutic procedural sedation, if required, must also be considered
- Use of a MC, PICC, CVC or portacaths in patients receiving active treatment and associated non-therapeutic procedural sedation, if required, is approvable under 21 CFR 50.52 as providing a prospect of direct benefit.

Applying Component Analysis to ESSENCE

- Patients who receive placebo with SRP-4045 and SRP-4053 do not directly benefit from participation in the study.
- Risks of MC, PICC, CVC or portacaths cannot be judged against the potential benefits of the drug if no drug is administered, and cannot be evaluated under 21 CFR 50.52.
  - Risks of procedural sedation, if required, must also be considered
- Use of a MC meets requirements under 21 CFR 50.53 as a minor increase over minimal risk.
  - Use of non-therapeutic procedural sedation is not required.

Applying Component Analysis to ESSENCE

- Use of a PICC, CVC or portacaths in patients receiving placebo and the use of associated non-therapeutic procedural sedation is not considered approvable under 21 CFR 50.53 as a minor increase over minimal risk and consequently a federal panel review under 21 CFR 50.54 is required.
  - Risk exceeds a minor increase over minimal risk
  - Procedures are not “reasonably commensurate” with expected medical situations
  - Procedural sedation is required

Question One (voting):

Use of an indwelling central venous access device in the ESSENCE clinical trial should be allowed.

Yes There are circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial.

No There are no circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial.

Question Two (non-voting):

If the ESSENCE protocol, as amended to include the use of an indwelling central venous access device, is allowed to proceed, please discuss the following issues:

a) Should the choice and timing of placement of a clinically-appropriate central venous access device be left to the discretion of the study site investigator?

b) Should the protocol include criteria for deciding when an individual study participant has difficulties with peripheral intravenous access (DIVA) such that use of a central venous access device may be appropriate?

c) If the protocol should include such criteria, what type of criteria ought to be specified (e.g., number of failed attempts at establishing peripheral intravenous access, number of visits where there was difficulty establishing peripheral intravenous access, use of alternative visualization technologies)?

d) How should the burden of undergoing multiple failed attempts at establishing peripheral intravenous access be taken into account (e.g., anticipatory anxiety, post-traumatic stress)?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