UCLA IRB FDA Referral on the ESSENCE Trial for Duchenne Muscular Dystrophy

James McGough, M.D., M.S.

Chair, UCLA Medical Institution Review Board

Professor, UCLA Division of Child & Adolescent Psychiatry

Joint Meeting of the U.S. FDA Pediatric Advisory Committee and Pediatric Ethics Subcommittee,

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Speaker Financial Support

- Travel to meeting paid by UCLA IRB
- No personal financial interests with study sponsor

Overview

- Background
- IRB Considerations
- IRB Conclusions
- Questions and Discussion

Background

06/11/15	ESSENCE submitted for review
06/23/15	Initial IRB review – deferred for consent issues
08/14/15	Full Board initial approval
08/01/16	Continuation approved – no enrollments to date
02/25/17	Parent complaint received
03/09/17	Full board IRB review of complaint

Summary of Complaint

- FDA guidance precluded use of port-a-cath as having risk without benefit for placebo group
- One UCLA participant's mother complained of "significant pain and stress" resulting from multiple attempts at IV access on multiple visits
- All 5 enrolled UCLA participants having difficulty with IV access
- 3 of 5 enrolled also with concomitant Autism and added difficulties tolerating IV placement

IRB Membership

- Child Psychiatry
- Community Representatives
- Genetics
- Neurology
- Nursing
- Oncology
- Pharmaceutical services
- Psychiatry
- Psychology
- Pediatrics

IRB Considerations

1. Board reviewed initial parental complaint and acknowledged risks of stress related to difficulties with recurrent IV placement in the study population over 96 week trial

IRB Considerations

2. Reviewed and discussed additional parental input including concerns about possible need to drop out of trial or obtain port-a-cath placement at own expense outside of study

IRB Considerations

3. Reviewed and discussed risks vs. benefits of port-a-cath vs. other access methods
    - Need for general anesthesia
    - Potential for clotting
    - Infection
    - Removal
    - Lifespan
    - Future use in open-label extension

IRB Considerations

4. Reviewed and discussed risks vs. benefits of alternative means of access, i.e. PICC line, central venous catheter, midline catheter
    - Need for general anesthesia
    - Potential for clotting
    - Infection
    - Removal
    - Lifespan
    - General anesthesia

IRB Considerations

5. Reviewed PI proposal to minimize port-a-cath associated risks

   - Use only in patients with demonstrated difficulty with IV access – 3 or more attempts at two consecutive visits or 5 or more attempts at one visit
   - Port placement only at sponsor approved sites with pediatric intensive care units by surgeons with extensive experience

IRB Considerations

6. Reviewed UCLA experience with port-a-cath-placement
    - Only performed in Clinical Translational Research Center (CTRC)
    - Occurrence of infection, thrombosis, post-operative complications rare
    - Parents trained to recognize infection
    - Port status monitored weekly
    - Single placement for course of study likely sufficient

IRB Conclusions

1. Board is concerned about the potential for weekly trauma and undue psychological risks over the course of study participation
2. Board recognized potential risk of iatrogenic PTSD – of particular concern in these patients who will require increased medical care over their lifetimes

IRB Conclusions

3. Risk of medically-induced trauma in study participates creates potential for early drop-out or termination of participation, further undermining likelihood of successful study completion

IRB Conclusions

4. Use of port-a-cath in participants who fail easy IV access has a preferable risk/benefit ration compared with other options for access

5. Appropriate means to decrease associated risks proposed and supported by empirical evidence

IRB Conclusions

6. Board open to determine that port-a-cath placement represents “minor increase over minimal risk” absent FDA’s previous prohibition
7. Board members saw no difference in port-a-cath risk in active vs. placebo groups
8. All participants have potential benefit from port-a-cath placement once rolled into open treatment

IRB Conclusions

9. Unanimous Board determination that ESSENCE investigation represents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children

IRB Conclusions

10. Use of port-a-cath per investigator's proposal would be acceptable to the IRB but for the FDA's previous determination

11. Recommended for referral to FDA under 21 CFR 50.54

Questions & Discussion