



Component Analysis

*Presentation to the Secretary's Advisory Committee
on Human Research Protections*

Robert 'Skip' Nelson, MD PhD
Senior Pediatric Ethicist/Lead Medical Officer

Office of Pediatric Therapeutics, Office of the Commissioner
Food and Drug Administration, Silver Spring MD

Robert.Nelson@fda.hhs.gov

Presented on February 29, 2012; slides updated for posting.

Disclaimer

- The views expressed in this presentation do not necessarily represent the policies of the Food and Drug Administration or the Department of Health and Human Services.
- I have no financial conflicts.

Topics

- What is “classic” component analysis?
- How is this “classic” approach to component analysis different from what is discussed in the published literature?
- Why is component analysis important?
- Current FDA guidance on the use of component analysis

Additional Safeguards

21 CFR 50, Subpart D

- Not involving greater than minimal risk (§50.51)
- Greater than minimal risk but presenting the prospect of direct benefit to individual subjects (§50.52)
- 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)
- Not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (§50.54)[†]
- Requirements for permission by parents or guardians and for assent by children (§50.55)

[†] Requires review by federal panel

What is “classic” component analysis?

- A clinical investigation may include more than one intervention or procedure.
- Each intervention or procedure must be evaluated separately to determine whether it does or does not hold out the prospect of direct benefit to the enrolled child.
 - This “classic” approach is consistent with the recommendations of the National Commission (1978) 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).

How is this “classic” approach to component analysis different from what is discussed in the published literature?

- “Component Analysis_w” (with equipoise)
 - as proposed by Charles Weijer and Paul B. Miller (in Nature Medicine, June 2004)
- “Net Risks” Test
 - as proposed by David Wendler and Frank G. Miller (in Journal of Medical Ethics, August 2007)
 - refers to “component analysis_w” as “dual track”

“Component Analysis_w”

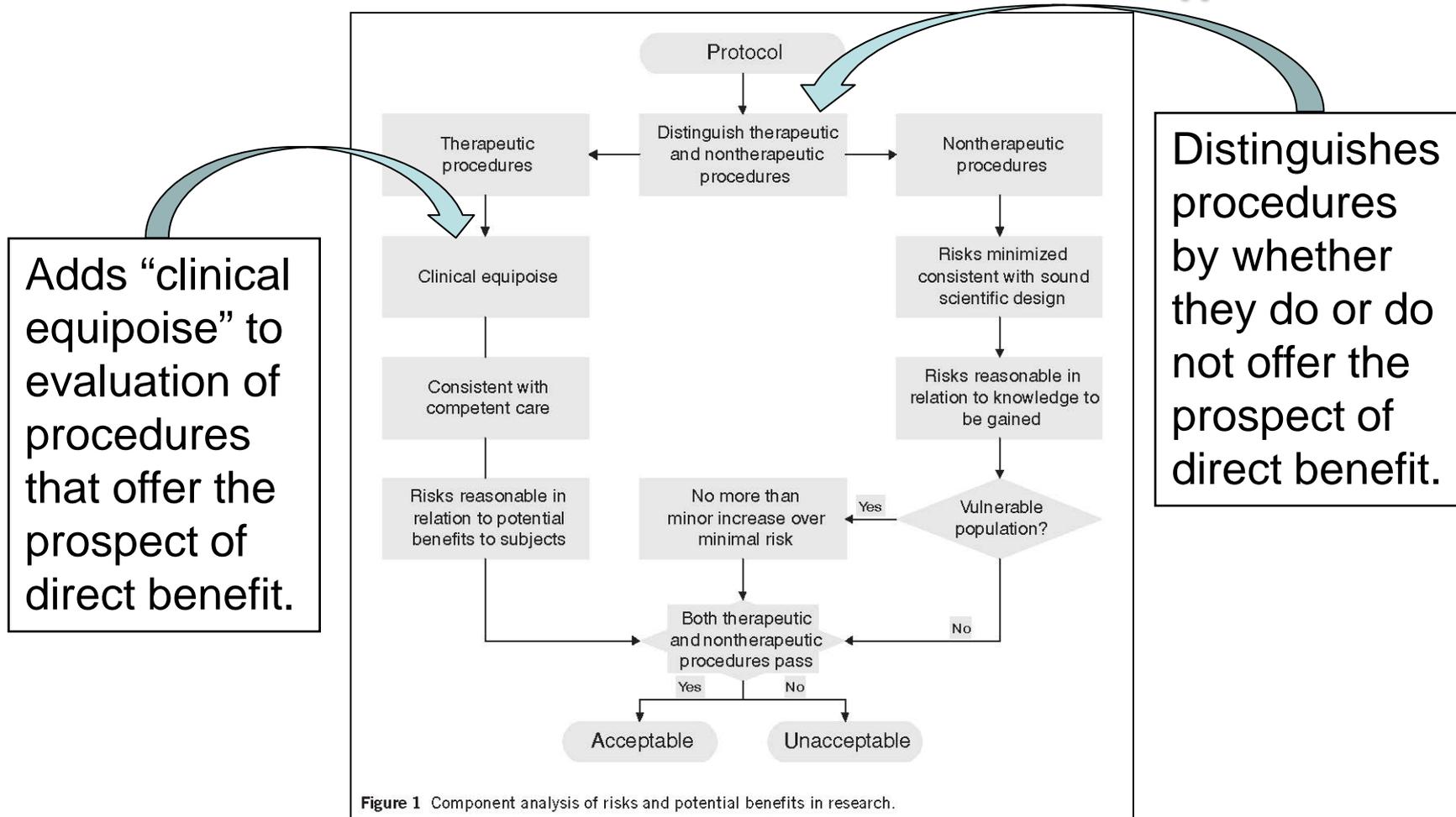
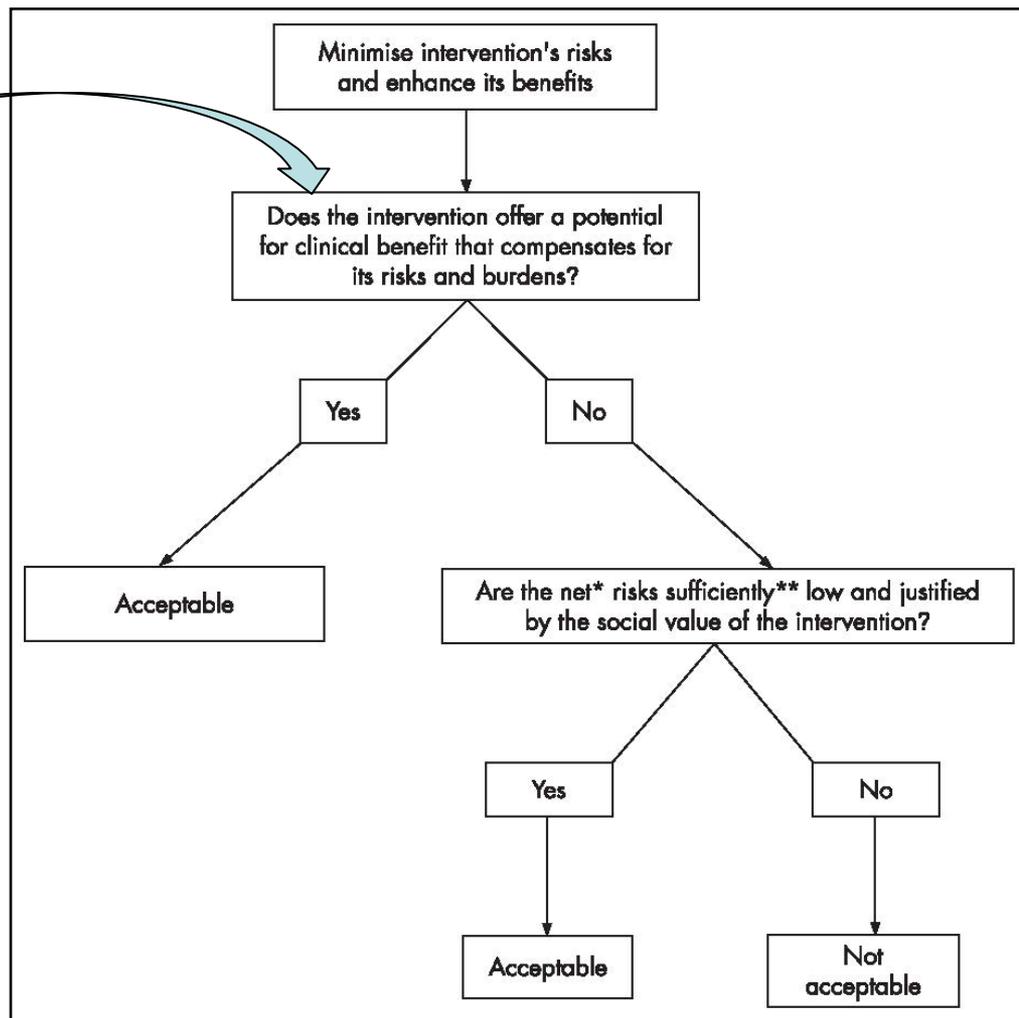


Figure 1 Component analysis of risks and potential benefits in research.

“Net Risks” Test

Distinguishes procedures by whether they do or do not offer the prospect of direct benefit.



Clinical Equipoise

- Combines two separate concepts
 - Adequate “uncertainty” to justify the clinical trial.
 - Known effective treatment should be provided to subjects (based on a fiduciary “duty of care”).
- Dispute about “component analysis_w” (“dual track”) is primarily about whether a fiduciary “duty of care” should be the ethical basis for clinical research.
- Criteria in 21 CFR 50.52 bear some resemblance to clinical equipoise, but do not entail that known effective treatment can never be withheld.

Assessment of the Debate

- Both the “dual track” (i.e., “component analysis_w”) and the “net risks” approach agree on the importance of assessing interventions or procedures individually as to whether they do or do not hold out a prospect of direct benefit.
- Neither approach offers advantages (and both have disadvantages) compared to a “classic” component analysis using the categories in 21 CFR 50 subpart D.

Why is component analysis important?

- 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).

Case Study: Background

- Multinational, placebo-controlled, study of an investigational product, in children ≥ 7 years old.
- Product (or placebo) administered (double blind) by IV infusion over 4 hours each day for 14 days.
- FDA Pediatric Ethicist called by a concerned IRB Chair about proposal to use a peripherally inserted central catheter (PICC) to facilitate infusion.
- Upon review, the protocol and supporting documents provided by the sponsor to the FDA review division never mentioned PICC use.

Consultative Role

- The FDA Pediatric Ethics program is located in the Office of Pediatric Therapeutics in the Office of the Commissioner.
- The program consults upon request to FDA product-related centers (CDER, CBER, CDRH, CTP, CFSAN).
- Decision-making authority resides with the requesting division or office, and all communication with regulated parties takes place through the division or office.
- Significant regulatory actions, such as the imposition of a clinical hold on a clinical trial, requires the approval of the responsible review team, division and office director.

FDA Assessment

- The insertion and use of a PICC for administration of the investigational product presented more than a minor increase over minimal risk.
- PICC use was justified in children receiving the active product due to the prospect of direct benefit from the infusion.
- Children receiving the placebo via PICC were offered no direct benefit from the infusion, but exposed to greater than a minor increase over minimal risk.
- Thus, PICC insertion and use in the placebo group was not in compliance with 21 CFR 50, subpart D.

Use of Clinical Holds in Pediatrics

- Criterion for a clinical hold under 21 CFR 312.42: Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury.
- 21 CFR 50 subpart D sets the standards for “reasonable” risk exposure in pediatric clinical trials.
- If the risks of an intervention fall outside of these standards, the intervention exposes the enrolled child to an “unreasonable and significant risk of illness or injury.”
- Thus, failure to be in compliance with 21 CFR 50 subpart D is sufficient grounds for imposing a clinical hold on a proposed or on-going pediatric clinical trial.

Corrective Actions

- Clinical trial had been suspended by the sponsor due to lack of product efficacy, so no future pediatric subjects were at imminent risk.
- FDA advised the sponsor that PICC utilization was not allowed for future pediatric subjects, and requested information from the participating IRBs.
- IRBs were asked whether PICCs had been used at each site, and if so, how PICC insertion was justified in the IRBs' assessment of the study.

Questions for IRBs

- How were the risks of PICC insertion and use, and the need for procedural sedation in some subjects, justified in the IRB's assessment of the approvability of the study under 21 CFR 50, Subpart D?
- Was the justification for PICC insertion and use different among subjects randomized to the placebo arm than for subjects randomized to the active treatment?
- What information about the risks of PICC use, including insertion and procedural sedation, was included in the parental permission and child assent forms?

IRB Responses

- PICCs used at 19 (of over 100) sites, approved by 12 IRBs.
- 10 of 12 IRBs answered FDA's questions.
- 9 of 12 reported a risk determination for the study
 - 7 of 9 IRBs approved both arms under § 50.52
 - 1 of 9 approved both arms as “more than minimal risk” (no category specified)
 - 1 of 9 approved the active arm under § 50.52 and the placebo arm under § 50.53
 - 2 of 9 used component analysis.

IRBs and Component Analysis

- Of the two (2/12) IRBs that used component analysis to assess the protocol, one applied the principle correctly but came to a different conclusion about the appropriateness of PICC use under 21 CFR 50.53, and the other applied component analysis incorrectly.
- We do not have information about IRBs (>80 sites) that did not approve PICC use, and thus do not know if they considered and rejected PICC use.

FDA's Response

- FDA provided a written analysis of the information and comments obtained from the IRBs (summarized in the back-up slides), explaining the application of component analysis and the risks that are allowable under 21 CFR 50.53.
- The letter (signed by the responsible division director) was sent to the sponsor, with instructions to disseminate it to all IRBs that participated in studies of the investigational product.

Current FDA Guidance (ABOM)

“The... ethics of placebo-controlled trials is addressed in... the ICH [E10]. With the possible exception of a superiority study of the investigational antimicrobial compared to another antimicrobial, the other types of superiority studies... may involve the withholding of known effective antimicrobial treatment. For such a clinical investigation to be approvable by a local IRB under 21 CFR part 50, subpart D, the risk to children randomized to a comparator arm that involves the withholding of known effective treatment (whether placebo or delayed therapy) must be no more than a minor increase over minimal risk (21 CFR 50.53).”

Current FDA Guidance (ABOM)

“Study sponsors should have in place mechanisms to assure that study centers performing tympanocentesis (and individuals at these centers) have sufficient experience and training to ensure that this procedure poses no more than a minor increase over minimal risk to patients (21 CFR 50.53). Alternatively, the availability of unblinded culture results so that effective antimicrobial treatment can be initiated in response to a treatment failure may provide a direct benefit to the enrolled children and thus be acceptable under 21 CFR 50.52.”

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070947.pdf>

Current FDA Guidance (ABOM)

“For an isolated single-dose PK study in children, sufficient evidence of drug safety from prior studies in adults would be needed so that the risk exposure for children is limited to no more than a minor increase over minimal risk (21 CFR 50.53). ...Based on a component analysis of risk, the PK component of [an] efficacy study would be acceptable, depending on the exact study design, either as minimal risk (21 CFR 50.51) or as a minor increase over minimal risk (21 CFR 50.53). If the PK data are used to adjust the dose of the study medication, an IRB may consider this aspect of the study as offering the prospect of direct benefit (21 CFR 50.52).”

Preamble to 2001 Interim Final Rule 21 CFR 50 subpart D

- “The agency also recognizes that the requirement for the prospect of direct benefit to individual subjects may create ambiguity about whether placebo-controlled clinical investigations may be conducted in children. FDA believes that clinical investigations involving placebos in children may be conducted in accord with § 50.52. There is evidence of direct benefit to subjects from participating in placebo-controlled trials, including increased monitoring and care of subjects, even though a subject may not actually receive the test product.”

Preamble to Final Rule

21 CFR 50 subpart D

- “In our discussion of § 50.52 in the preamble to the interim rule (66 FR 20589 at 20593), we ...noted that there is evidence of direct benefit to children from participating in placebo-controlled trials, including increased monitoring and care of subjects, even though a child may not actually receive the test product. This statement has been misinterpreted, and we provide clarification in the paragraphs that follow.” (emphasis added)

Preamble to Final Rule

21 CFR 50 subpart D

- “The general consensus of the [FDA Pediatric Ethics Subcommittee of the Pediatric Advisory Committee, meeting in June 2008] was that the placebo arm of a trial cannot be considered to confer the prospect of direct benefit under §50.52... In general, the PES advised that the so-called “inclusion” benefit is not a “direct” benefit, and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk.”

Preamble to Final Rule

21 CFR 50 subpart D

- “FDA agrees with [the Pediatric Ethics Subcommittee’s] position. Because we do not consider the administration of a placebo to offer a prospect of direct benefit, part 50, subpart D, therefore requires that the placebo arm must present no more than minimal risk (§ 50.51) or a minor increase over minimal risk (§ 50.53), unless the clinical investigation is referred for review under 21 CFR 50.54.”

78 Federal Register 12937-12951 (February 26, 2013)

Preamble to Final Rule

21 CFR 50 subpart D

- “A placebo-controlled study of an investigational drug or biologic may involve the withholding of known effective treatment (section 2.1.3, ICH E 10). In such situations, however, the risks of such withholding of known effective treatment in the placebo control group should present no more than minimal risk or a minor increase over minimal risk, i.e., the placebo control arm of such a clinical trial must be approvable under either § 50.51 or § 50.53. The arm that receives the investigational product often would be approvable under § 50.52.”

Topics Covered

- What is “classic” component analysis?
- How is this “classic” approach to component analysis different from what is discussed in the published literature?
- Why is component analysis important?
- Current and future FDA guidance on the use of component analysis



Thank you.



Backup Slides

- FDA provided a written analysis of the information and comments obtained from the IRBs, explaining the application of component analysis and the risks that are allowable under 21 CFR 50.53.
- The following slides outline that analysis.

IRB Responses: Justification for PICC Use

- Parents and children were given a choice about whether to use PICC catheters or peripheral IVs.
- All subjects have the possibility of directly benefiting if randomized to active treatment.
- PICCs offer less discomfort and are easier to insert than multiple venipunctures.
- PICCs are standard-of-care for children with difficult venous access.

FDA Analysis: Parental Choice?

- The implication that PICC insertion may be appropriate if parents and children choose to use it undermines the intended protective function of 21 CFR 50 subpart D and abdicates the responsibility of IRBs.
- 21 CFR 50 subpart D caps the risk that parents may allow their children to assume for non-beneficial procedures at a “minor increase over minimal risk.” It is the IRBs’ role to ensure that these safeguards are followed at each site.

FDA Analysis: All subjects may benefit?

- If the prospect of direct benefit is attributed to all subjects prior to randomization, it is impossible to do an individual assessment of the risks and benefits of each intervention or procedure individually as required by 21 CFR 50 subpart D.
- Absent this approach, children could be exposed to excessive risk from non-beneficial research procedures simply by adding other beneficial procedures (such as warranted health care) to the protocol

FDA Analysis: Ease of Use?

- Discomfort does not alter the potentially serious risks of PICC use, and the procedural sedation that may be necessary for insertion.
- To use this discomfort as a justification inappropriately ignores these risks.
- If establishing venous access is difficult in conventional pharmacokinetic studies, children are routinely withdrawn from the research given that the intervention does not offer a prospect of direct benefit.

FDA Analysis: PICCs as Standard-of-Care?

- PICC use is “standard of care” only when use of these catheters offers the child a prospect of direct benefit (children would not receive a PICC in clinical practice absent a potential benefit of the infusion).
- In the current study, 50% of the enrolled children would be infused with placebo. The infusion of placebo does not offer a child a prospect of direct benefit from the infusion, because (by definition) the placebo is physiologically inactive.

IRBs and Component Analysis

- Of the two IRBs that used component analysis to assess the protocol, one applied the principle correctly but came to a different conclusion about the appropriateness of PIC catheters under subpart D, and the other applied component analysis incorrectly.

One IRB's Analysis

- “For subjects receiving placebo, the study met the requirements of 45 CFR 46.406 and 21 CFR 50.53...The placebo arm was approvable based on the finding that the study procedures represented only a minor increase over minimal risk.”
- Children on active treatment were approved under 45 CFR 46.405 and 21 CFR 50.52 as having a prospect of direct benefit.

Another IRB's Analysis

“The placebo arm of the randomized clinical trial was not treated as a separate non-therapeutic intervention (a la Miller and Brody)...[the placebo arm] was treated as a “substitute” for an active treatment intervention and both placebo and active treatment were evaluated against the standard of best available alternative treatments...If it is not known at the outset of the trial whether the risk-benefit ratio of the placebo arm will be more or less favorable for subjects than the active treatment arm, then the requirements of 21 CFR 50.52 are satisfied.”

FDA Response

- To treat the placebo arm as a “substitute” for an active treatment intervention appears to be equivalent to a pre-randomization analysis discussed earlier.
- The fact that one is uncertain at the start of a trial whether the intervention arm will be better than placebo does not mean that the placebo can be viewed as offering a prospect of direct benefit.

Information in Most ICFs

- The disclosed risks of PICC insertion included “catheter occlusion (blood clot in the tube), phlebitis (inflammation of the vein), hemorrhage (excessive bleeding), thrombosis (blood clot in your vein) and infection.”
- The disclosed risks of procedural sedation included: “low oxygen and low blood pressure, allergic reaction, aspiration (taking food or fluid into the lungs), or in very unusual circumstances, death.”

Limitations of Disclosed Information

- The difference in magnitude of risks for a PICC compared to a peripheral IV catheter were not discussed, or the risks of PICC insertion were inappropriately minimized as being “similar to an IV”.
- Procedural sedation was sometimes considered “minimal risk”, despite disclosures noting that procedural sedation carries a small risk of death.