Exception from Informed Consent in FDA/CBER Clinical Trials

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CBER: Center for Biologics Evaluation and Research

CBER's mission:

to protect and enhance the public health through the regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies.

Outline

- Federal regulations
- 50.24 studies reviewed at CBER
- Transfusion product considerations
- Study design
- Study conduct
- Summary

Federal Regulations: 21 CFR 50.24

"*Exception from informed consent requirements for emergency research*"

- Limited class of research: Subjects in life-threatening situation; available treatments unsatisfactory/unproven
- Justify: Obtain scientific info in consenting subjects? Study less sick pop'n? Prospectively identify subjects?
- Death likely if disease course not interrupted; intervention needed before consent is feasible
- Participation has prospect of direct benefit
- Community informed/consulted
- IRB and DMC oversight required

Example: 50.24 Studies(1)

Life-threatening trauma

- Patient commonly unconscious
- Uncontrolled hemorrhage
- Intervention at trauma site or ED
- SoC at trauma site
  - start fluids ASAP on site
  - blood components transfused upon arrival to hospital ED

Example: 50.24 Studies$_{(2)}$

Investigator's Objective: Determine if *modification* of product transfusion improves outcomes

- Earlier setting (i.e., pre-hospital) of same products administered in ED
- Different product administered pre-hospital
- Same products administered in ED but in different quantity

Example: 50.24 Studies(3)

- Focus on pre-hospital and early hospitalization interventions; recognize the critical importance of this time frame
- Generally research studies without commercial purpose
  - Sponsored by DoD, NHLBI, or Resuscitation Outcomes Consortium
- FDA required to review the studies even if the study therapies are FDA licensed products that will be used within the scope of standard practice of medicine
  - thawed plasma, platelets, RBCs, hypertonic solution

Transfusion Product Considerations

- Blood products/components are a resource for the entire country, not a product just used or manufactured for a clinical trial
- Impact blood supply and demand; and potentially blood banking policy and practice
- Have the right blood type available (AB+ 3-5% prev)
- Very limited shelf life of blood components (plasma: 5 days once thawed); minimize waste
- Reporting/tracking requirements, e.g.,
  - Transfusions/transfusion reactions
  - Look back (virus transmission)

The exception from informed consent in trials for transfusion products can influence the study design and conduct.

Study Design(1)

- Overall
  - Parallel arm, active control (SoC)
  - Superiority hypotheses
- Primary Endpoint
  - Prospect of the intervention providing direct benefit
  - 1-month mortality (or co-primary endpoint)
- Sample Size
  - Good effect size assumptions are critical
  - Sensitivity analyses around effect size assumptions
  - Allocation of blood bank's supply to the study

Study Design(2)

- Randomization
  - Which subject enrolled if multiple eligible subjects
  - Individual (ambulance) vs. cluster (helicopter)
  - Cluster analysis increases sample size (more subjects w/ no informed consent) & potential for baseline characteristic imbalance
- Mid-study assessments
  - Internal feasibility study: assess operational and safety issues
  - Interim analyses: futility, efficacy, and/or safety

Study Design(3)

- Logistics
  - Opt-out mechanism
  - Field-to-ED transport time
  - Unblinded at trauma site (transfusion of blood products requires documentation). Blinded at ED?
  - Blood products
    - Transportation to trauma site
    - Proper storage (where, how, monitoring)
    - Rotation of blood product (frequency)
    - Return of unused products into blood supply

Study Conduct(1)

Many of the same issues as any other clinical trial, but the subject protection "bar" is higher.

Study Conduct(2)

- Recording of data
  - Study data generated pre-ED (who and how?)
  - Blood component tracking data
    - Storage, temperature monitoring, administration
    - Transfusion reaction
- Missing data
  - Primary endpoint of 1-month mortality => need to track down outcome
  - Prevent it; acceptable amount missing?
  - Data is retained for subjects who later refuse consent

Study Conduct(3)

- Oversight
  - Data Monitoring Committee (review unblinded data to adequately balance risks and benefits)
  - Medical monitor (DoD requires)
  - Audits (who, what, frequency)
- Training
  - Higher accountability: key personnel certification
  - Special attention to EMTs

Main Points

- The exception from informed consent and the use of transfusion products influences the study design and conduct
- Carefully manage and track the blood component resource
- Subject protection “bar” is higher