

RESEARCH ETHICS LECTURE SERIES

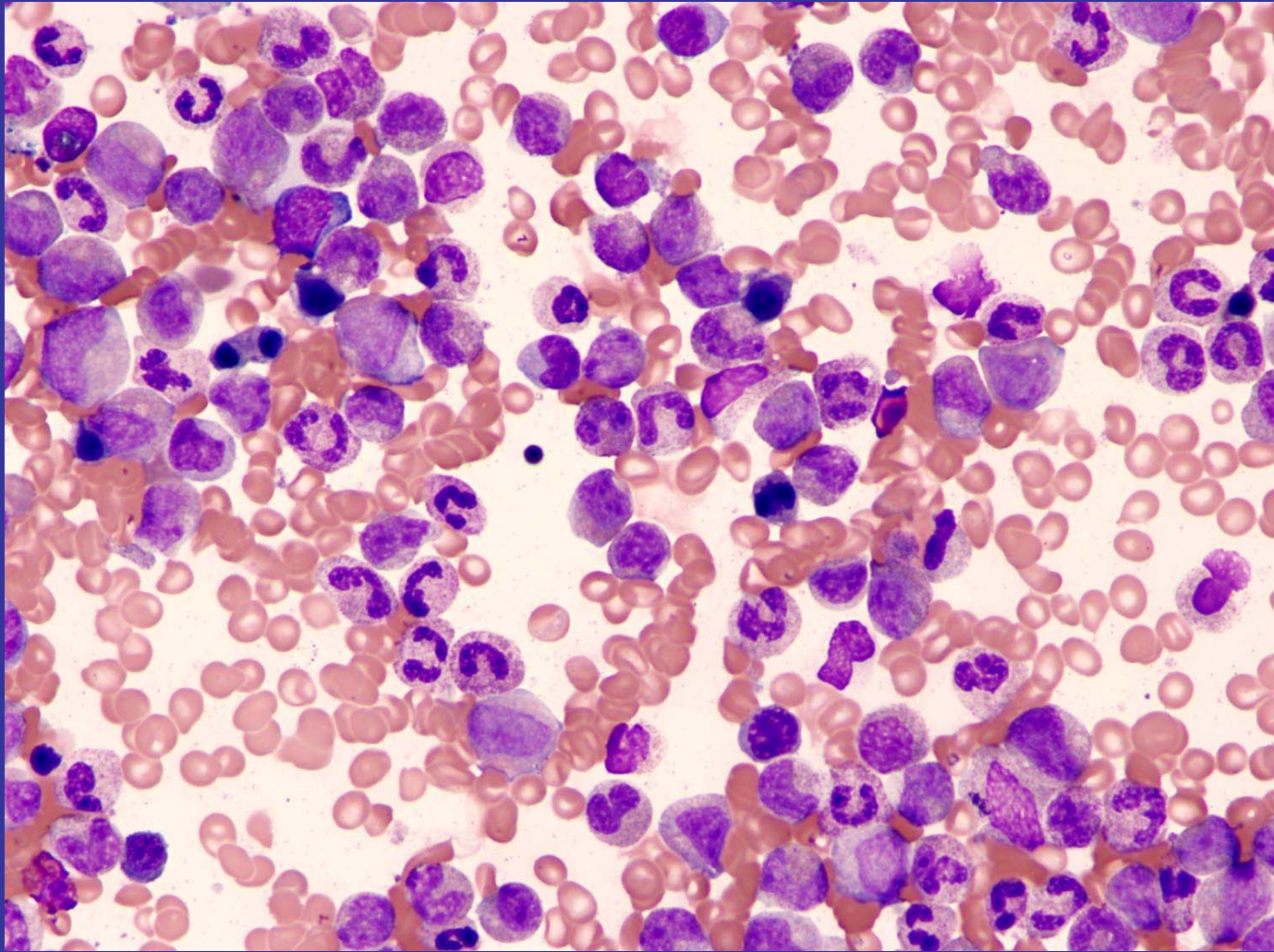
March 8th, 2007

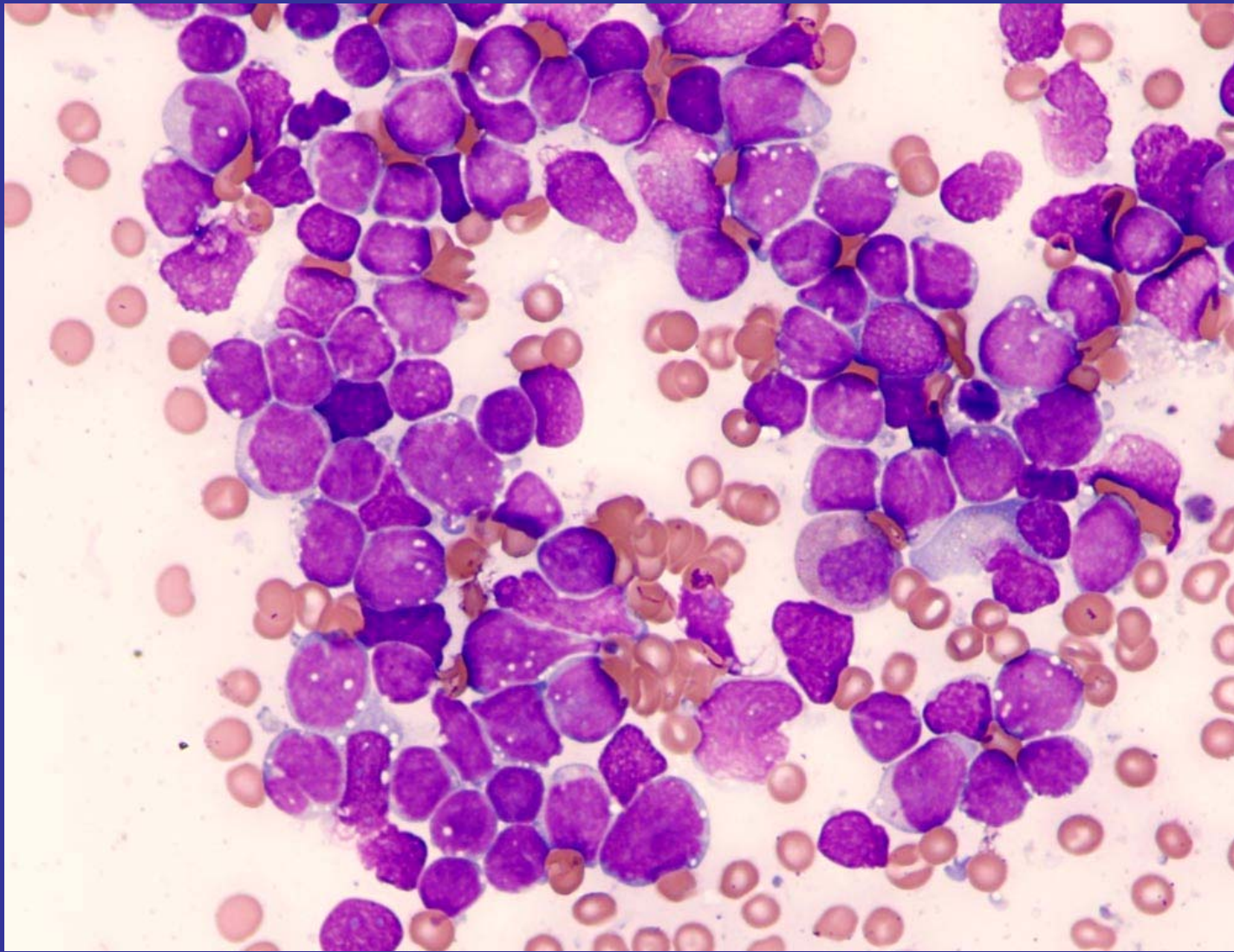
“INFORMED CONSENT ISSUES IN
PEDIATRIC CANCER RESEARCH”

Dr. Melvin H. Freedman

OPENING REMARKS

- 70% of pediatric cancer patients in N.A. enroll in clinical trials.
- Studies show: for all parents giving consent for their children, true informed consent not achievable in every research situation.
- Study in 2001: 1/2 children with cancer not aware they were in a research clinical trial.





CONQUEST OF PEDIATRIC ALL RESEARCH ACHIEVEMENTS

- Central nervous system prophylaxis
- Chemotherapy drugs in combinations
- “Pushing” drugs to toxicity
- Improved supportive care
 - Antibiotics; fever-neutropenia Rx
 - Blood products
 - Cytokines and growth factors
- Identification of risk and prognostic categories
 - WBC count and age at diagnosis
 - Blast morphology, phenotype, cytochemistry
 - Blast cytogenetics and molecular profile

RESEARCH ACHIEVEMENTS (continued)

- Most patients are treated in pediatric oncology centres
- HSCT as firstline Rx or salvage Rx
 - Phenotype and genotype donor matching
 - Family donors
 - Matched unrelated donors
 - Umbilical cord blood, matched and mismatched
- Multicenter study groups
- Introduction of IRB's and REB's in 1970's
 - High scientific standards
 - Safeguards for protection of research subject
 - Regulatory compliance
 - Adherence to ethical principles

CASE REPORT

HISTORY OF ILLNESS

- 14 yr male admitted with fever
- History of
 - pallor, fatigue
 - Shortness of breath on stairs
 - Bruising, loss of appetite
- Lost consciousness on stairs
 - 911 → community hospital
 - CT scan of head → normal
 - Routine blood test
 - » “hyperleukocytosis”
 - » Low hemoglobin – anemia
 - » Low platelets – bruising

CASE REPORT (cont'd)

Transferred to Sick Kids' PICU

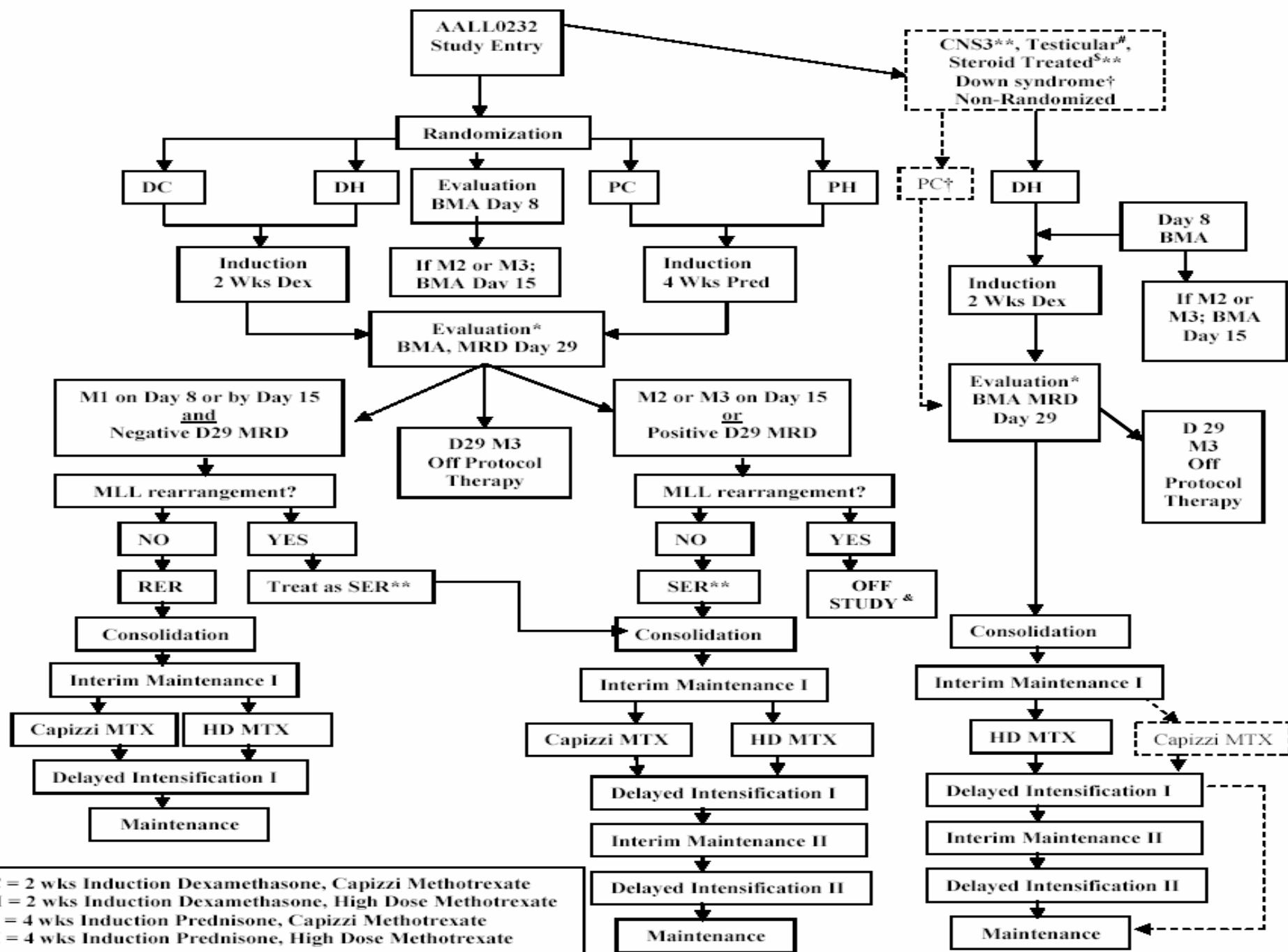
- Admission tests
 - white blood cells: 10 x normal (stroke!)
 - hemoglobin: 1/3 normal
 - platelets: not detectable
 - abnormal chemistries
- Leukopheresis to reduce white cells but,
 - cardiac arrest
 - resuscitated

CASE REPORT (cont'd)

Additional Testing

- Bone marrow: 99% leukemic blasts
- Refined testing
 - » Acute lymphoblastic leukemia
 - » Molecular studies: t (4;11), AF4 fusion gene (mixed lineage, infant leukemia)

EXPERIMENTAL SCHEMA



RESEARCH IN HIGH RISK ALL

- Not possible to obtain fully informed consent from parents
 - Capacity to understand
 - Adequate information
 - Voluntariness
- Not possible to obtain assent from child
 - Definition difficult

ADEQUATE INFORMATION DIFFICULT TO CONVEY

- New language of cancer
- Complicated implications of:
 - Hyperleukocytosis, TLS risk
 - MLL gene
 - Double randomization
 - SER
 - MRD
 - HD MTX vs. Capizzi
 - Non-randomization criteria
- Distinguishing therapy from research

CLINICIAN'S PREMISE

- Not possible to obtain fully informed consent or assent from the child in this scenario...

.....but does it matter?

RESEARCH IN HIGH RISK ALL

- Is there a moral obligation to conduct research in this context?
- Does it matter that parents or child are not fully able to provide consent/assent?
- Is this situation any different from most of the other clinical trials we conduct in pediatric oncology?

TriCouncil Policy – Canada (Section 5 and Article 5.8) Inclusion in Research

- Section 5 - Principle of Distributive Justice means neither an unfair burden nor an unfair exclusion from the potential benefits of research
- Article 5.3 Those not competent to consent for themselves, shall not automatically be excluded from research that is potentially beneficial to themselves as individuals, or to the group they represent.

TriCouncil Policy – Canada (Article 2.8) Research in Emergency Health situations

Consent waiver if:

- Serious threat to person and,
- No standard treatment, or potential direct benefit and,
- Risk of harm no greater than standard or justified by direct benefits and,
- Subject lacks capacity and,
- Third party authorization cannot be secured in time and,
- No relevant prior directive of subject known.

OHRP Letter Regarding Waiver of Informed Consent in Emergency Situations (1996)

8 elements including IRB oversight

- Life threatening situation
- Informed consent not feasible
- Prospect of direct benefit
- Research not practical without waiver
- Condition not identifiable prospectively
- Informed consent documents available
- **Window of therapy defined
- ** Consultation with communities affected (non-binding)

SOME CRITICAL COMPONENTS OF FREE AND INFORMED CONSENT (Section 2, TCPS)

“...lies at the heart of ethical research involving human subjects...”

(Section 2.1d)

“...must be voluntarily given, without manipulation, undue influence or coercion...”
(Section 2.2)

- Subject must have capacity to understand content, and appreciate consequences.
- Written consent forms must:
 - ❖ be easy to read and be a sensible length for parents and older patients
 - ❖ be understandable at a grade 6 level
 - ❖ distinguish between clinical and research procedures
 - ❖ explain risks and benefits
 - ❖ explain voluntary nature of enrollment
 - ❖ contain complete information
 - ❖ be totally consistent with the protocol
 - ❖ are clear about withdrawal conditions
 - ❖ disclose COI

CHILDREN'S CAPACITY TO UNDERSTAND

Journal

Findings

J Med Ethics
2005;31:715-20
understand concepts

- Using age-appropriate modules of information 6 yr olds can understand of risks vs benefits.

Am J Public Health
1978;68:1079-82

- 6 yrs olds have difficulty understanding future benefits arising from a research intervention.

Ethics Behav
1995;5:24-48

- 7 yr olds have difficulty understanding “confidentiality” and “voluntariness”.

CHILDREN'S CAPACITY TO UNDERSTAND (cont'd)

Journal

Findings

J Med Ethics
1998;24:158-65

- 8 yr olds or < poorly understand concept of clinical trials.

Child Dev
1982;53:1589-98

- 9 yr olds have difficulty with hypothetical treatment dilemmas.
- 14 yr olds are as competent as adults.

ADULT'S CAPACITY TO UNDERSTAND

Journal

Findings

N Engl J Med
1980;302:896-900

- 80/200 cancer pts didn't understand purpose/nature of chemo, XRT, surgery 24 hrs after signing consent
- 90/200 could not list one major risk of Rx

West J Med
1975;123:76-80

- 80% who gave informed consent for a clinical trial forgot risks of interventions after enrolling

Am J Ophthalmol
1979;87:620-3

- Of 100 retinal detachment pts undergoing surgery
- 43 forgot pre-op disclosure
 - 77 forgot surgical risks
 - 39 forgot suture discussion

ADULT'S CAPACITY TO UNDERSTAND (cont'd)

Journal

Findings

J Natl Cancer Inst
1998;90:668-74

- std SWOG consent (college senior) compared to simplified version (7th grade) :
comprehension identical for both

US Dept of Education
1993;"Adult Literacy
In America"

>20% of US adults have limited
reading skills

RESEARCH ETHICAL ISSUES IN PEDIATRIC ONCOLOGY

- Same person wears two hats
 - ❖ distinctions between roles are blurred
 - ❖ voluntary free-informed consent doubtful
 - ❖ “points” for COG enrollments
- Same person has COI's
 - ❖ paid consultant to pharmaceutical firm
 - ❖ firm sponsors consultant's research
 - ❖ consultant owns shares in firm
- Patients with cancer are easily misled
 - ❖ blurred distinction between research and therapy
 - ❖ coercion and enticement : access to research treatment only possible by enrolling in the protocol
 - ❖ Decision-making is impaired as disease progresses: unrealistic expectations

RESEARCH ETHICAL ISSUES

(continued)

- Patients with cancer are vulnerable
 - ❖ placebo-control studies
 - ❖ donate tissue for banking
 - ❖ donate tissue for genetic studies
 - ❖ allow open-ended collection for health data after study closes
 - ❖ financial obligations to patients/families
- Disclosure and informed consent issues
 - ❖ 1-2 hour disclosures
 - ❖ distinguishing clinical from research components
 - ❖ 15-20 page written consents
 - ❖ comprehension level of written consents
- Phase I pediatric oncology trials
- Mandatory CCRN registry enrollment or no access to COG

RESEARCH ETHICAL ISSUES IN PEDIATRIC STEM CELL TRANSPLANTATION

- Informed consent: an oxymoron
- Assent not legally allowable in USA if decision is detrimental
- Sibling donor issues
 - ❖ refusal
 - ❖ risks if agrees to donate
 - ❖ emotional burden if transplant fails
 - ❖ lowered esteem if sibs not asked to donate
- Transplants for QOL
 - ❖ sickle cell
 - ❖ thalassemia
 - ❖ DBA
- Conceiving a child for spare parts
- Choosing embryos for spare parts

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