Ethics and Realities in SMA Research and Emerging Therapies

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Make today a breakthrough.

Disclosure

- Roche (Switz) and Genetech (US) Pharmaceuticals, advisory panel research design and outcomes for intervention trials in children with SMA – Rob Graham
- Audentes Pharmaceuticals, advisory panel research design and outcomes for intervention trial in children with XLMTM – Rob Graham
- Biogen Pharmaceuticals, SMA advisory panel– Rob Graham; Ethics consultation, Tom Murray

- Commercial Sponsorship: None

Objectives for this Session

- Explore ethical, emotional and pragmatic issues related to medical research

- Review types and phases of research
- Review historical background to research ethics and regulations the pharmaceutical companies (and private entities) goals and expectations
- Discuss goals and expectations of stakeholders (researchers, pharmaceutical companies, clinicians, subjects, hospitals,…)
- Consider your goals and expectations

- Open Discussion

Captured by History: The Nuremberg Doctor's Trial

- The first sentence of the first principle in the Code could not be clearer: "The voluntary consent of the human subject is absolutely essential."
- Three further conditions:
- that the individual have legal capacity to give consent;
- that they be able to do so freely and without coercion;
- and that the person "should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him/her to make an understanding and enlightened decision."

Declaration of Helsinki

1964 Declaration of Helsinki of the World Medical Association issued a series of “recommendations” to guide research on human subjects

(Revised at regular intervals over many years)

- “**The interests of the subject must always prevail over the interests of science and society**.”

- “In any medical study, every patient--including those of a control group, if any--should be assured of the best proven diagnostic and therapeutic method."

National Research Act, 1974

The Act created the **National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research**.

Charge: identify the basic ethical principles that should underlie the conduct of biomedical and behavioral research involving human subjects

- Boundary between research and care
- Risk-benefit assessment
- Guidelines for subject selection
- Nature and definition of informed consent

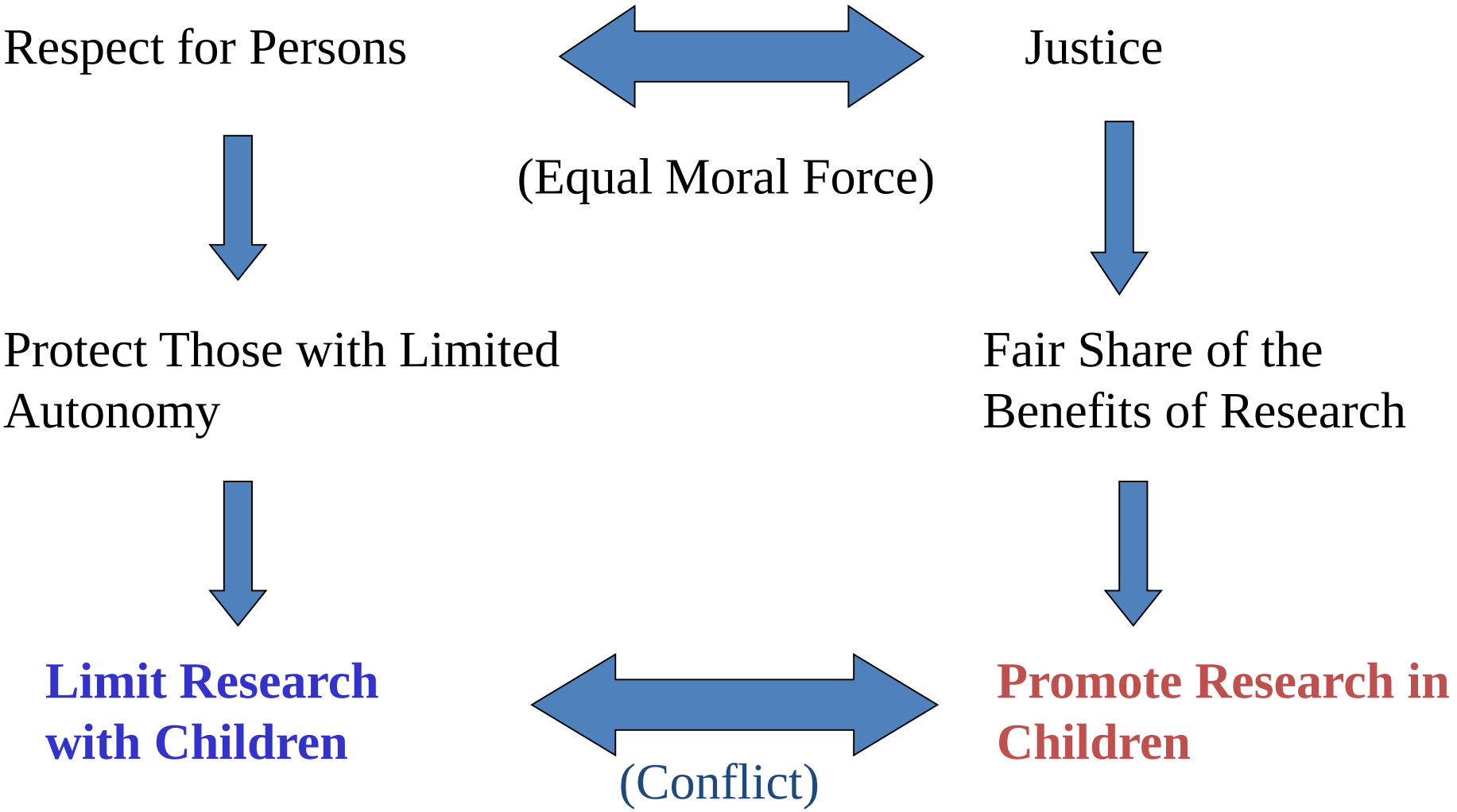
Belmont Report 1979

- **Respect for persons** as **autonomous individuals** with right to self determination
  - obtain informed consent, protect privacy and confidentiality
- **Beneficience**
  - do no harm, provide benefit, limit risks
- **Justice**
  - equitable selection of subjects
  - equitable distribution of risks and benefits.

Applying The Belmont Report

- **Respect for Persons = Informed Consent**
  - Recognition of the autonomy of persons
  - Protect those with diminished autonomy
- **Beneficence = Risk/benefit analysis, minimize risks**
  - An obligation to do good, not simply kindness or not harming
  - Maximize possible benefits, minimize possible harms
- **Justice = Fair selection of research subjects**
  - Distribution of the benefits/burdens of research
- **IRB system expanded**

Conflict in Belmont Principles for Kids?



What's At Stake: The Example of Pediatric Cancers

- 50 years ago nearly all pediatric cancers were fatal
- Thanks to research, ~80% now with at least 5 year survival
- Children's Oncology Group (NCI funded)
- >90% of children and adolescents in US treated at a member institution
- ~70% of children diagnosed with cancer are enrolled in a clinical trial
- COG includes institutions in US, Canada, Switzerland, Netherlands, Australia and New Zealand
- Children with cancer enrolled in RCTs fare better than those who do not enroll.
- Children cared for by pediatric oncologists at centers that participate in clinical trials tend to have improved outcomes—both those who enroll in trials and those who do not. Reasons include access to novel treatments, more rigorous clinical follow-up and monitoring, and a readily available diverse group of pediatric oncology experts.

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Risk/Benefit Analysis in Research Involving Children

- Not involving greater than **minimal risk**. (45CFR46.404)
- Involving **greater than minimal risk**, but with the **prospect of direct benefit**. (45CFR46.405)
- Involving **greater than minimal risk**, **no prospect of direct benefit**, but likely to **yield generalizable knowledge** about the subject's condition. (45CFR46.406)
- Not otherwise approvable (45CFR46.407)

Protecting Research Participants

Jesse Gelsinger, 1999

- 18 year old with OTC deficiency (metabolic condition)
- Previously well-controlled with diet and oral medications
- Died 4 days after administration of adenovirus **vector** for gene therapy for OTC deficiency (U.Penn)

Ellen Roche, 2001

- 24 year old technician at Johns Hopkins Hospital Asthma and Allergy Center
- Administered hexamethonium as part of an asthma study
- Died of respiratory failure

What Informed Consent Accomplishes with Adults

- Demonstrates respect for the research volunteer's personhood
- Ramsey: investigator and subject as "coadventurers"
- Powerful safeguard against exploitation and harm
- Accommodates individual preferences in relation to risk and the desire to help others
- These are not accomplished to comparable degree, if at all, in children

Parents & Children:
Expanding our Moral Horizons

- Chicken pox and Christmas pageants…
- Frantic mothers and Cleveland snowstorms…
- Our duty to protect our children from harm, while deep and profound, does not trump all other duties and goods we are justified in seeking.
- As children develop capacities to act as moral agents, parents have a duty to teach them about their responsibilities to others: family, community, fellow sufferers of disease. In doing this we show respect for our child.

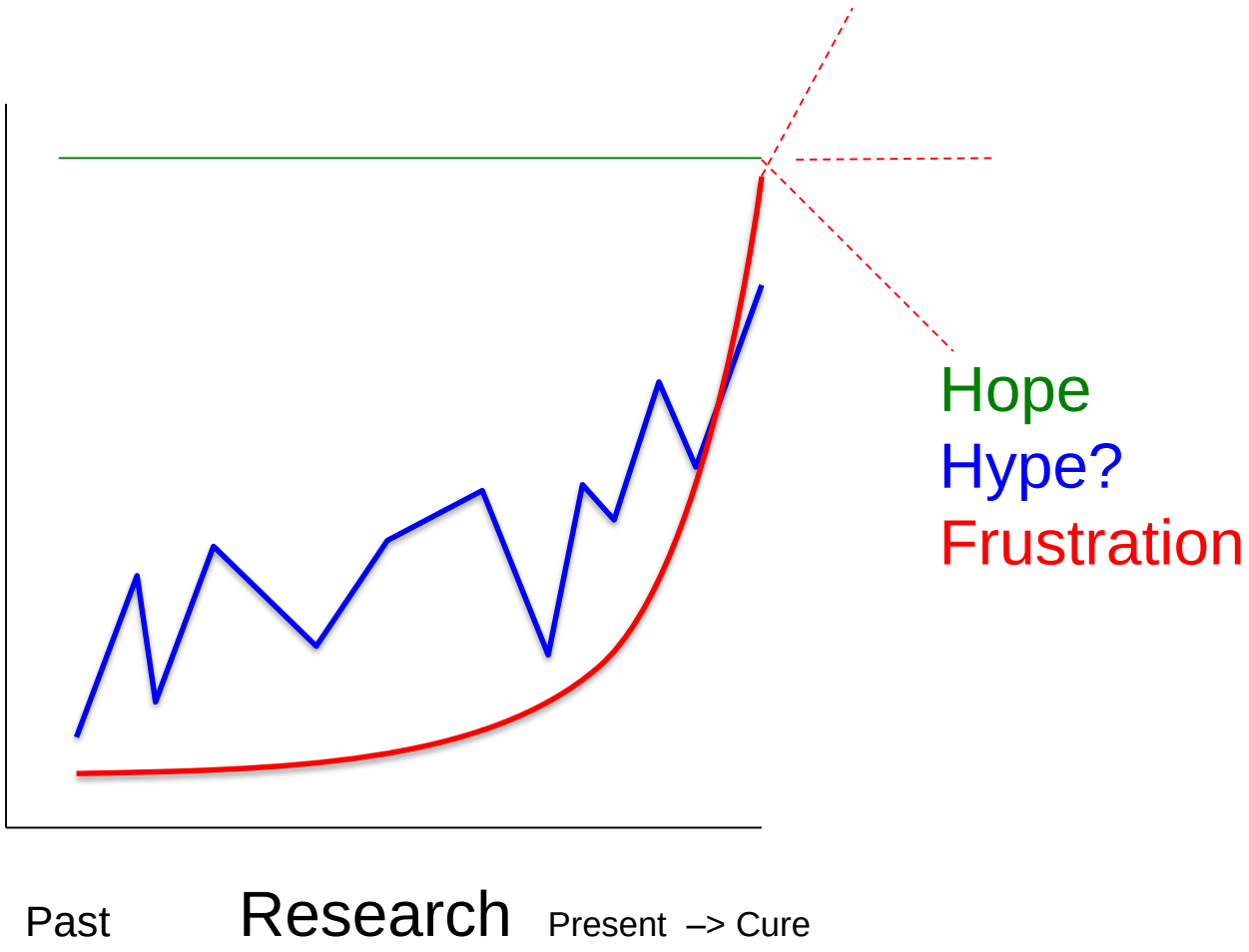
Some Cautions in Applying these Analogies to Participation in Research

- Sad history of exploitation, including children
- Parents may be overly deferential to scientists
- Parents of gravely ill children may be desperate
- Therapeutic Misconception may mislead parents
- Researchers' motives may be complex
- -Jesse Gelsinger, gene therapy for OTC

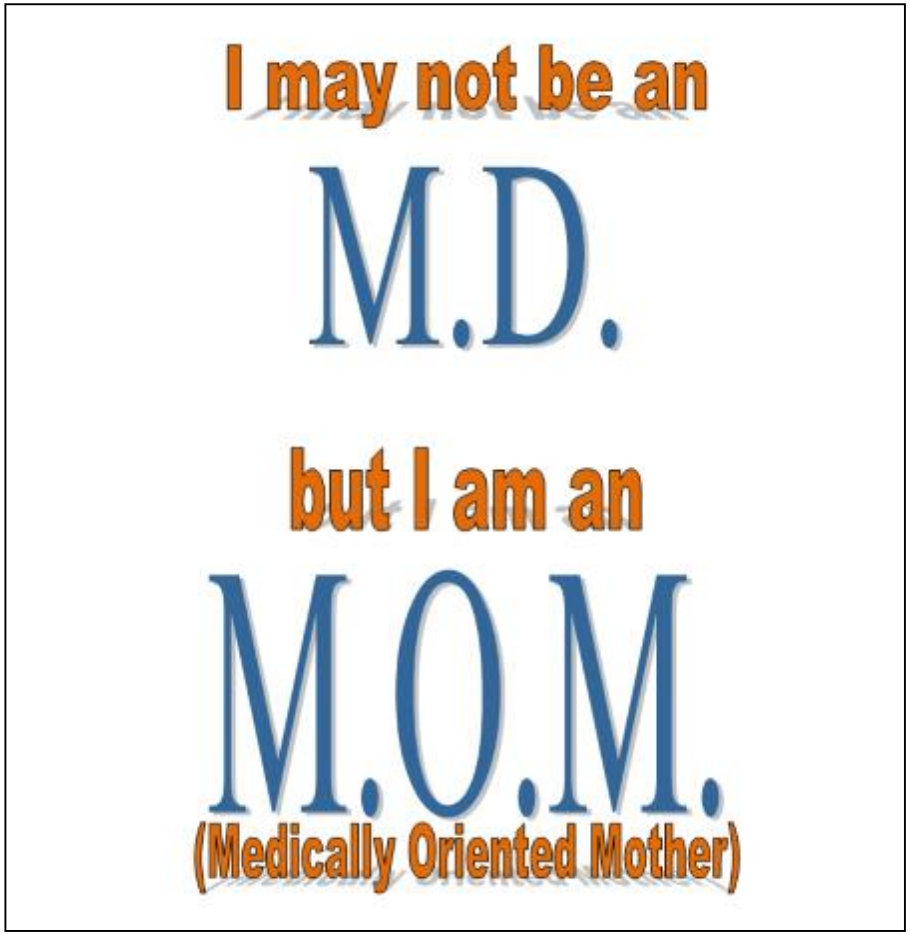
In Sum

- Be clear about your ethical reasoning and principles
- Informed consent simply cannot do all the moral heavy lifting for research on children
- Focus on doing what is required to protect them
- Focus also on doing whatever we can to demonstrate our respect for them

Patient / Family Experience: Correlation Model



A changing landscape for care and research ethics


I may not be an
M.D.
but I am an
M.O.M.
(Medically Oriented Mother)

Research

- Treatment / “Clinical Trials”
- Prevention
- Diagnostics
- Screening*
- Quality of Life / “Supportive Care”*
- Genetic Studies
- Epidemiological Studies*


SPEED LIMITS
DAY — REASONABLE & PRUDENT
TRUCK — 60
NIGHT - ALL VEHICLES - 55

- “ An investigational drug is a substance that, when given to a rat or research subject, produces a paper”

Different Paradigms … Same Providers?

- Medical Therapy
  - Targeted at individual
  - May be adjusted
  - Objective is treatment of your symptoms / condition
- Medical Research
  - Target population/study group
  - Protocol adherence
  - Interest in global results – statistical significance

Research by the book

Investigational New Drug/Therapy and the FDA

- Phase I: **Safety, dosage**, metabolism, and excretion
  - 1a – **Healthy volunteers**
  - 1b – Effected subjects **"proof of concept"**
- Phase II: **Efficacy** (vs. placebo?, blinding?) and side effects (individuals with the condition)
- Phase III: **Dose variation** to determine efficacy and adverse reactions, +/- combination with other known therapies – Large numbers of participants
- Phase IV: Post-marketing studies 1) compare to other drugs, 2) long-term risk vs. benefits, and 3) cost effectiveness

Yes, it is research

- **Therapeutic misconception**: Research subject may not understand that the purpose of a Phase I trial is research
- **Therapeutic misestimation**: Research subject may overestimate their chances of personal benefit from the research
- **Therapeutic optimism**: Research subject is hopeful, "thinking positively" that Phase I trial will offer benefit

Additional Research Pragmatics and Considerations

- Understanding the Protocol
  - Eligibility (inclusion / exclusion) – why?
  - "Wash-out" of other therapies
  - Confidentiality
  - Blinding?
  - Commitment of participants
  - Incentives (monetary, prioritization, …) and disincentives
  - Projected risks
  - Side effects – contingencies and reparations

Additional Research Pragmatics and Considerations

- Parent as parent vs. IRB as parent
- External Review Boards – Safety
- Clinicians to provide unbiased clinical care
- Conflict of interest
- Funding sources (for-profit, not-for-profit, individuals, …)
- Compassionate-use protocols / Expanded Access
- ClinicalTrials.gov

Some Things to Consider

- **Possible benefits:**
  - access to new treatments not yet available
  - expert medical care during trial
  - helping others by contributing to research
- **Possible risks:**
  - side effects
  - treatment may not work
  - time for trips to the study site, treatments, hospital stays
  - stress and cost for the whole family
  - more complex dosage requirements
  - new treatment may not be available to you after trial

http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/deciding-participate-clinical-trial

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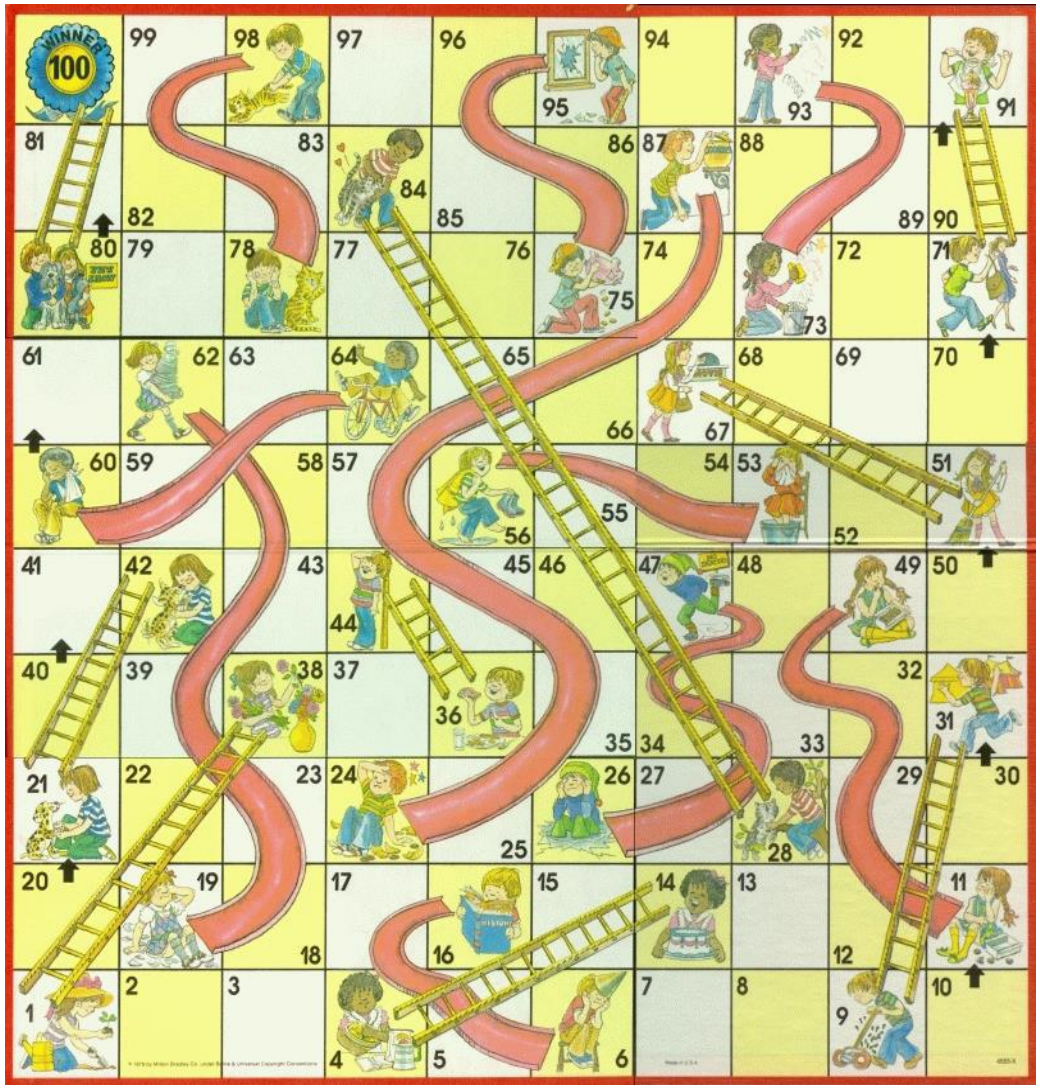
If it were only that simple

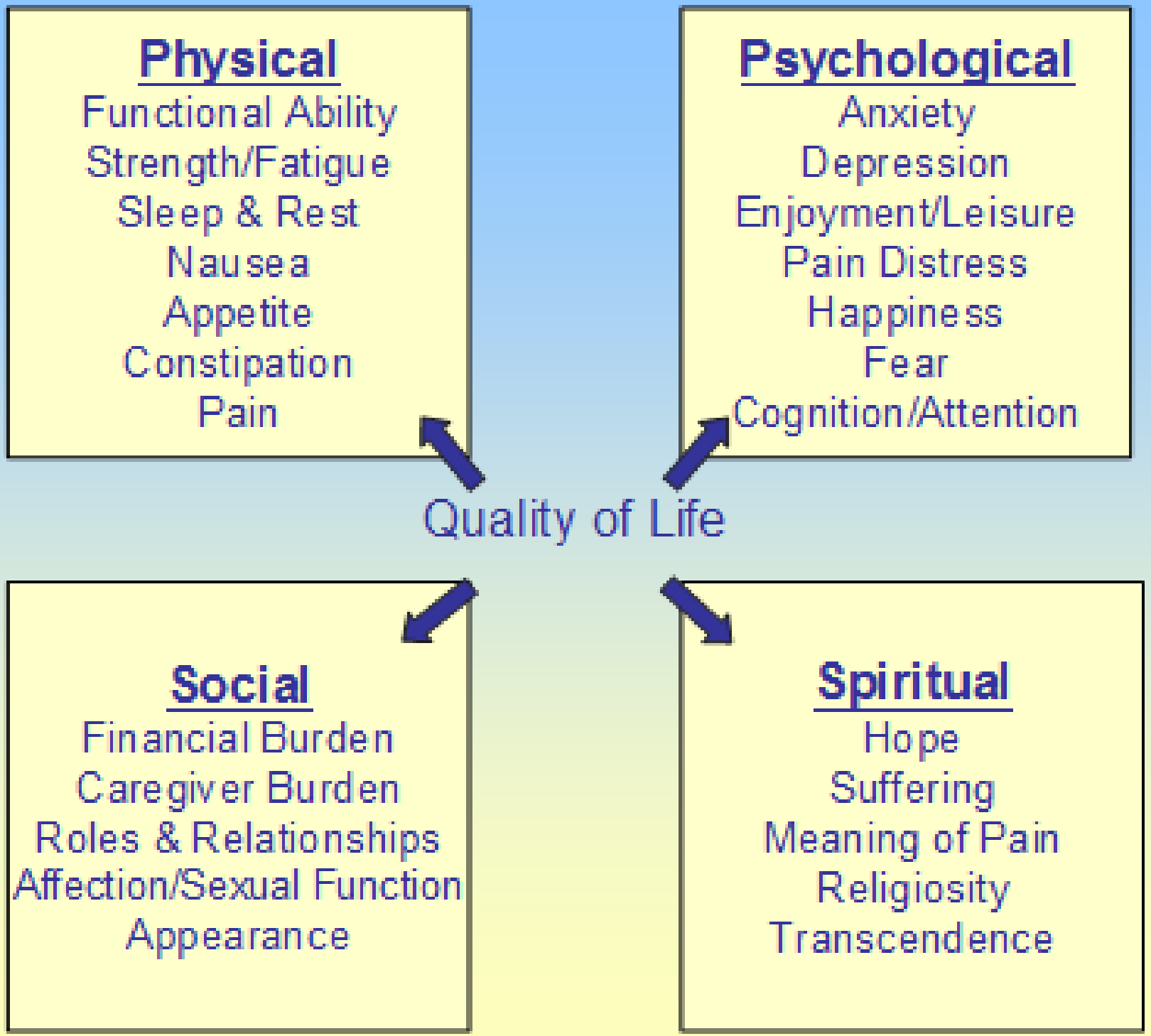
- Type overlap
- The enemy of good is perfect
- Prenatal screening and relation to research
- Maintaining therapy after completions of trial
- The last trial
- The next trial
- Size of population
- Clinical interventions/decision-making and exclusion (e.g., gastrostomy or spinal fusions)

Finding your path



What Are the Options?

- Families should make choices that are consistent with their personal beliefs and values and which work best for them.



Adapted from Ferrell, et al. 1991

Studies About Participating in Research

- Primary influences for Phase I trials
  - Hope for a cure
  - Trusting the physician’s (oncologist's) advice

- Surprise that anyone would participate in research for altruistic reasons

Oncol Nurs Forum. 2000 Oct;27(9):1435-8

Benefits and Risks of Clinical Trials

- Similar to making decisions about treatment
- Pros and cons
- Consider the risks – different for everyone

http://www.cancer.net/navigating-cancer-care/how-cancer-treated/clinical-trials/deciding-participate-clinical-trial

New Considerations

- What ethical implications, if any, have changed now that a medication has been approved by the FDA?
- Should you still consider clinical trial participation for your child?
- Do the risks of the unknown change?
- How does eligibility for participation change?

Revisiting Our Objectives

- Explore ethical, emotional and pragmatic issues related to medical research

- Review types and phases of research
- Discuss the pharmaceutical companies goals and expectations
- Discuss goals and expectations of the site investigators and hospitals
- Identify your goals and expectations

- Open Discussion