ENGELBERG CENTER for
Health Care Reform
at BROOKINGS

Accelerating Drug Development for Sickle Cell Disease

Washington Plaza Hotel• Washington, DC
Thursday, October 9, 2014

Sickle Cell Disease (SCD)

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Sickle Cell Development

Development of safe and effective treatments for preventing and reducing the complications of sickle cell disease

FDA Mission

- protect the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices.
- responsible for the safety and security of most of our nation’s food supply, all cosmetics, dietary supplements and products that give off radiation.
- responsible for regulating tobacco products

INDs and NDAs

- INDs – Investigational New Drug Applications – application made to the federal government for clinical research
- NDAs/BLAs – marketing application – application submitted to get a product approved for widespread use by the public

INDs

- Average number of INDs submitted per year from 1995-2004 – 5
- Average number of INDs submitted per year from 2005-present – 8.5

- NDAs – 1 (approved 1998)

Regulatory Mechanisms

- Fast Track
- Break Through
- Special Protocol Assessment
- Orphan Designation
- Expanded Access
- Expedited Review
- Priority Review
- FDASIA

Fast Track

- Requirements
  - Serious Condition/Life-threatening Condition
  - Available Therapy
  - Unmet medical Need

Fast Track Submission for Sickle Cell Disease

- Data with justification
- Link to changes in the putative biomarkers to sickle cell disease activity parameter/manifestation (i.e., must be distinct from other disease areas)

Breakthrough

- Requirements
  - Serious Condition
  - Available Therapy
  - Unmet Medical Need
- Clinical Evidence

Special Protocol Assessment

- Three types of Protocols
- Carcinogenicity
- Stability
- Clinical Protocols intended to form the primary basis for an efficacy claim

Orphan Designation and Grant Funding

- Orphan Drug Designation
- Humanitarian Use Device
- Two Extramural Grant Programs
  - Orphan Products Grants Program
  - Pediatric Device Consortia Grants Program

Ongoing FDA Orphan Grants for SCD

Title	Sponsor	Site
Phase 2 Study of Vitamin D for Prevention of Respiratory Complications from Sickle Cell Disease	Gary Brittenham	Columbia University, Children's Hospital of NY
Phase 2 Study of T-Cell Depleted Familial Haploidentical SCT for the Treatment of High-Risk Sickle Cell Anemia	Mitchell Cairo	New York Medical College
Phase 2 Study of Aes103 (5-HMF) for the Treatment of Stable Sickle Cell Disease	Warren Stern	Aesrx, LLC
Phase 2 Study of SelG1 for the Treatment of Sickle Cell Disease	Scott Rollins	Selexys Pharmaceuticals Corporation
Phase 2 Study of Montelukast for the Treatment of Sickle Cell Anemia	Michael DeBaun	Vanderbilt University

Expanded access

- Allows access to drugs or biological products in development for compassionate use prior to widespread commercial marketing
- Emergency INDs, Single Patient INDs

  physician working with a pharmaceutical sponsor

  process which includes providing documentation, letters, etc.
- Requires pharmaceutical company to agree

FDASIA

- FDA initiated a five-year Patient Focused Drug Development program to learn from patients about the impact of their disease on their daily lives. FDA plans hold at least 20 public meetings over the next 5 years, each focused on a different disease area, and we expect that these gatherings will be attended not only by our staff and patient representatives, but also potential sponsors of new drug development.

FDASIA and Sickle Cell

- February 7, 2014 - Patient-Focused Drug Development (PFDD) for Sickle Cell Disease (White Oak)
- Today's meeting

What did we learn from PFDD for sickle cell

- Acute Pain Crisis
- Chronic Pain
- Fatigue
- Cognitive Effects- Difficulty Concentrating (school)
- Wider range of symptoms – temperature sensitivity, sleep disturbance, hearing

Approval

- Accelerated or Regular
- Accelerated
  - Affect a surrogate endpoint other than mortality or irreversible morbidity
  - Surrogate endpoint must be reasonably likely to predict clinical benefit, based on epidemiologic, therapeutic, pathophysiologic, or other evidence
  - Additional studies confirming clinical benefit must be completed after approval

Review

- Standard
- Priority
- Expedited

Facilitating Drug Development for Sickle Cell Disease

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Scientific Liason Sickle Cell Disease and Anticoagulants
Medical Officer
Division of Hematology Products
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Office of New Drugs
Center for Drug Evaluation and Research

Overview of trial design and regulatory considerations for clinical trials in sickle cell disease

Ideal Trial Design

- Comparator trials -- not single arm trials
- Multi-center trials
- Randomized, double-blind are preferred
  - Stratified randomization between arms
  - Balanced arms
- Statistical Analysis Plan
  - Well thought out ahead of time
  - Hierarchical testing for primary and secondary endpoints

Clinical Trial Efficacy Endpoints

- What Question are you Asking?

- Choosing a clinical endpoint will depend on **Stage of Development** (what question is being asked?)
  - Is the drug active **in sickle cell disease**? (early phase development)
  - Does it provide meaningful benefit? (late phase development)
- *Combining the goals of early and late phase development into one clinical study can be challenging.*

Strength of Efficacy Endpoint Results:

- **What** is being Measured**? (Endpoint Selection)**
  - Measures of Direct Benefit are preferred
- **How** accurately is it being measured**? (Measurement Characteristics)**
  - How certain can we be regarding the result and magnitude?
  - Susceptibility to Bias
    - The more interpretation required for an event, the more susceptible it is to bias.
- **How Much** effect on the endpoint is observed? **(Magnitude of Effect)**
  - Large effects seen in trial results can mitigate some uncertainty associated with an endpoint
- **Supportive** Secondary Endpoints

Endpoints from Sponsors

- Composite or single endpoints can be used for approval
- PK/PD, Safety, and Efficacy must be assessed in the sickle cell disease population
- Use established criteria if possible (or criteria likely to be accepted by a majority)
- If novel endpoint provide support/justification

Pediatric Drug Development in Sickle Cell Disease

- Safety must be established prior to enrollment of children in clinical trials
  - Non-clinical data **or**
  - Clinical trials in adults
- Efficacy endpoints
  - Considerations can be made for age of patient and relevance of treatment for each cohort (ex. Less than 2 years of age)
  - Recruitment considerations

Some of the endpoints considered

- Chronic use, Reduction in…
  - *Rate of Hospitalization*
  - *Rate of VOC*
  - *Acute Chest Syndrome*
  - *Pain (VAS score change, pain diaries)*
  - *Analgesic usage*
  - *Rate of RBC transfusion due to SCD*
  - *Reduction in school absence*
  - *Incidence of stroke*
- Acute use
  - *Length of pain crises*
  - *Length of hospitalization for VOC*

Droxia

- Randomized, double blind, placebo-controlled
- 299 adult patients (≥ 18 years)
- Moderate to severe disease (≥ 3 painful crises yearly)
- Trial stopped by DSMC after accrual completed but before scheduled 24 month follow up due to results.

Significant effect on primary endpoint and multiple secondary endpoints

Event	HU (N=152)	Placebo (N=147)	Percent Change	P-value
Median yearly rate of painful crises	2.5	4.6	-46	0.001
Median yearly rate of painful crises requiring hospitalization	1.0	2.5	-60	0.0027
Median time to first painful crisis (mths)	2.76	1.35	+104	0.014
Incidence of chest syndrome	56	101	-45	0.003
Number of patients transfused	55	79	-30	0.002
Number of units of blood transfused	423	670	-37	0.003

Issues Regarding Trial Endpoints

- What are the sources of heterogeneity in the patient population that may impact the endpoints? How do we manage?
  - Baseline severity, genotypic differences (SS, SB+, SC), modulators of disease
- What endpoints denote clinical benefit?
- What endpoints are reasonably likely to predict clinical benefit?

Note: Identify appropriate baseline severity so that a benefit of your drug can be appreciated

Lessons learned from past successful and unsuccessful trials

- Baseline disease severity important
- Must take into account the current practice of hematology (hospital vs. outpatient setting)
- Considerations of add-on designs (to hydroxyurea)
- A lot of institutional heterogeneity in day-to-day treatment and the acute management

Lessons learned, continued

- Consider how the information will be captured and any challenges with accurate data collection
- Plan for adverse event capturing that still incorporates the events that happen with sickle cell disease
- Consider early on how to handle missing data during the trial…*it happens.*
- Drugs that target underlying disease and not symptoms are needed

Summary

- FDA is committed to facilitating drug development for sickle cell disease
- Trial design and endpoint selection are key for success
- Excited about the opportunities that exist and the number of development plans in varying stages.
- We hope this meeting will continue the dialogue needed to translate trials into success.

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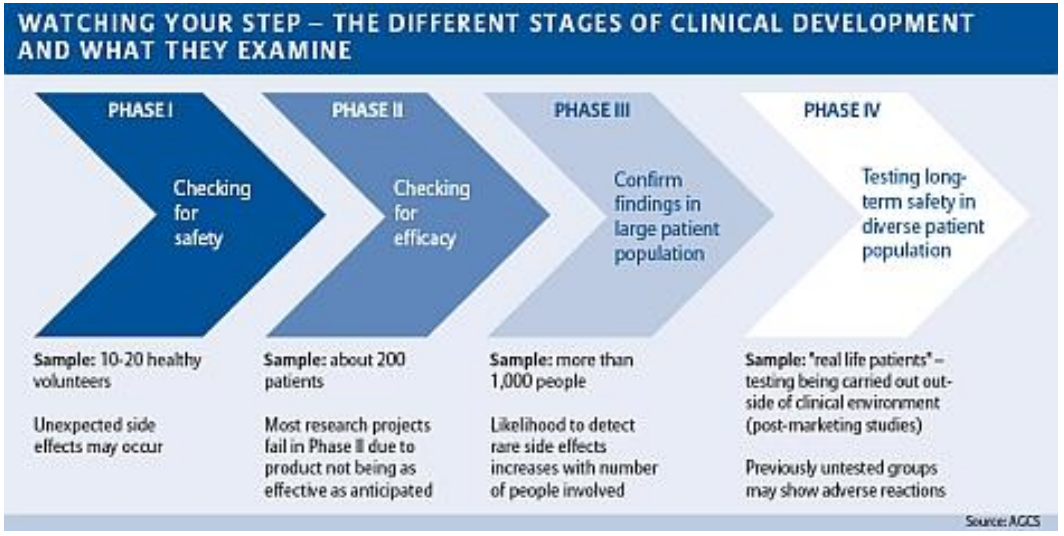
Sickle Cell Disease Clinical Trial Endpoints: A Framework



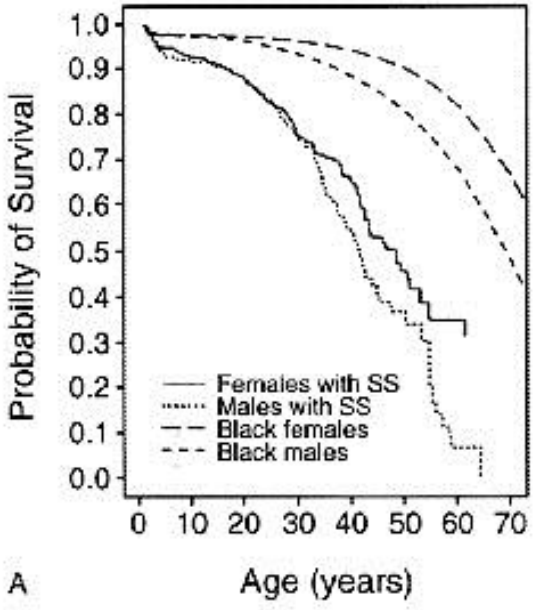
VCU Medical Center
Virginia Commonwealth University

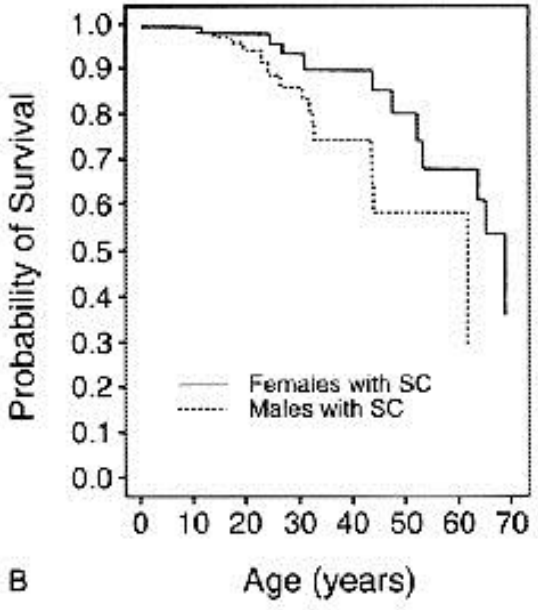
Wally R. Smith, MD
Florence Neal Cooper Smith Professor of Sickle Cell Disease
Virginia Commonwealth University

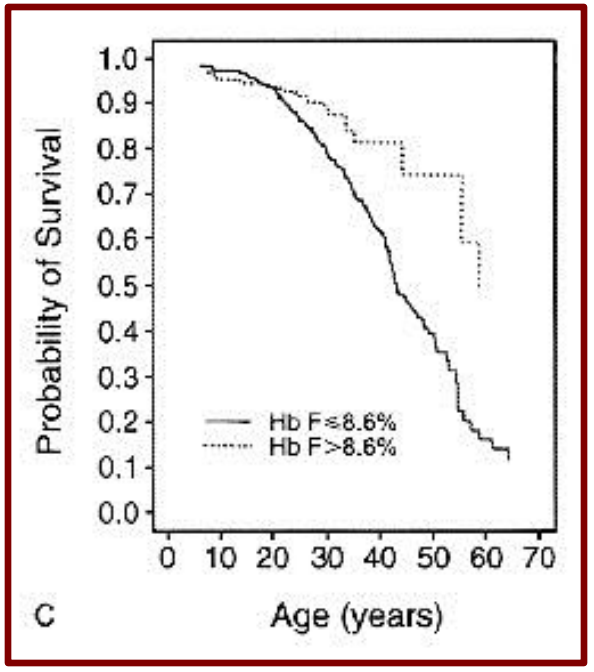
SCD Manifestations

- Pain
- Anemia
- Fatigue
- Utilization
- Acute organ damage
- Chronic organ failure

Survival of Patients in the Cooperative Study of Sickle Cell Disease

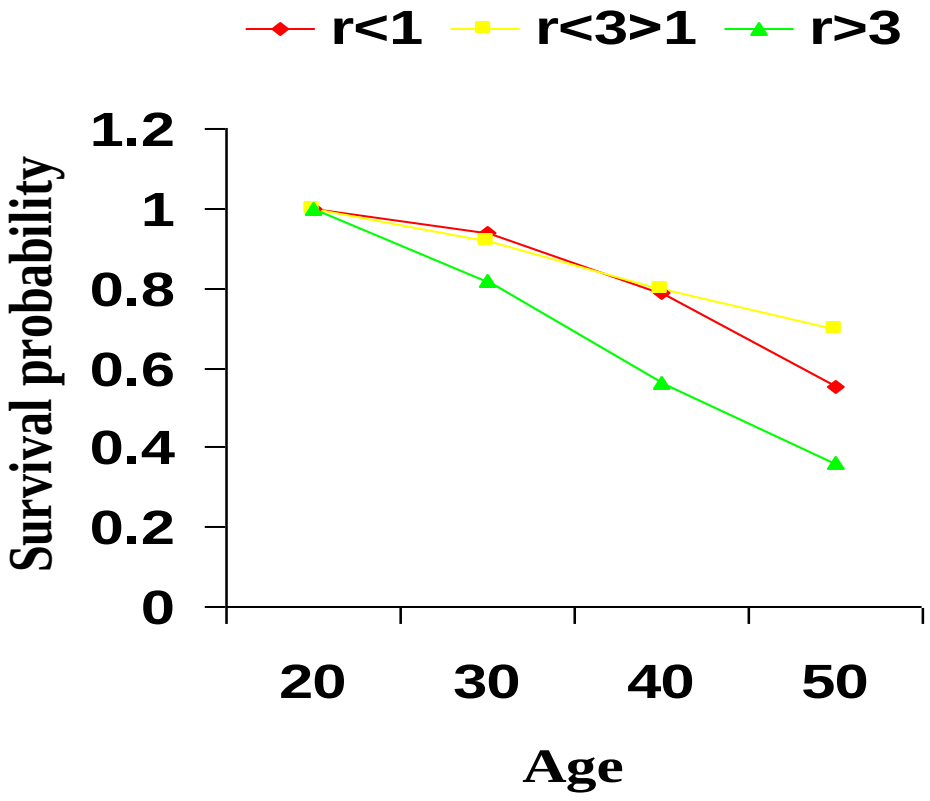






Platt OS et al. N Engl J Med 1994;330:1639-1644.

Results of CSSCD: “Pain” rate above age 20 predicts death



- Adapted from: Platt, et.al. N Engl J Med; 1991;325:11-16.

Summary of Poisson Model for Pain [Utilization] Rate in Sickle Cell Anemia [Hb SS]

Table 5. Summary of Poisson Model for Pain Rate in Sickle Cell Anemia.

Variable	Parameter Estimate*	Standard Error	Chi-Square (df)	P Value
Intercept	−2.3190	0.8378		
Age (yr)				
5–9	0	—	16.47 (5)	0.006
10–19	0.3631	0.1399		
20–29	0.5729	0.1703		
30–39	0.3785	0.2109		
40–49	−0.0973	0.2994		
≥50	−0.1641	0.5142		
Fetal hemoglobin level, squared	−0.0032	0.0008	16.57 (1)	<0.001
Hematocrit	0.0860	0.0158	29.59 (1)	<0.001
Sex				
Female	0	—		
Male	−0.3044	0.1036	8.70 (1)	0.003

*The parameter estimates can be used to calculate the predicted average pain rate (episodes per year) for any group of patients in the standard reference clinic with certain defined variables. The model equation is pain rate = exp[−2.3190 + age-group estimate − 0.0032 (fetal hemoglobin)^2 + 0.086 (hematocrit) − 0.3044 (if males)].

Platt OS et al. N Engl J Med 1991;325:11-16.

Correlations between Fatigue and Biological and Behavioral Variables in SCD

Variable	BFI Total	MFSI-SF Total	PROMIS
BPI worst	0.65***	0.40**	0.41***
BPI average	0.51***	0.48***	0.31*
BPI interference	0.55***	0.45***	0.42***
PSQI 0.53***	0.51***	0.47***	
STAI – State	0.44***	0.70***	0.45***
STAI – Trait	0.38**	0.55***	0.35**
CESD 0.42***	0.45***	0.45***	
PSS 0.41***	0.69***	0.37**	
Hemoglobin	−0.18	−0.03	−0.30*
log IL-1b	−0.10	−0.18	−0.13
log IL-6	0.20	0.06	0.17
log IL-10	−0.19	0.01	0.09
log TNF-α	−0.11	−0.18	0.03
Age 0.24	0.14	0.07	

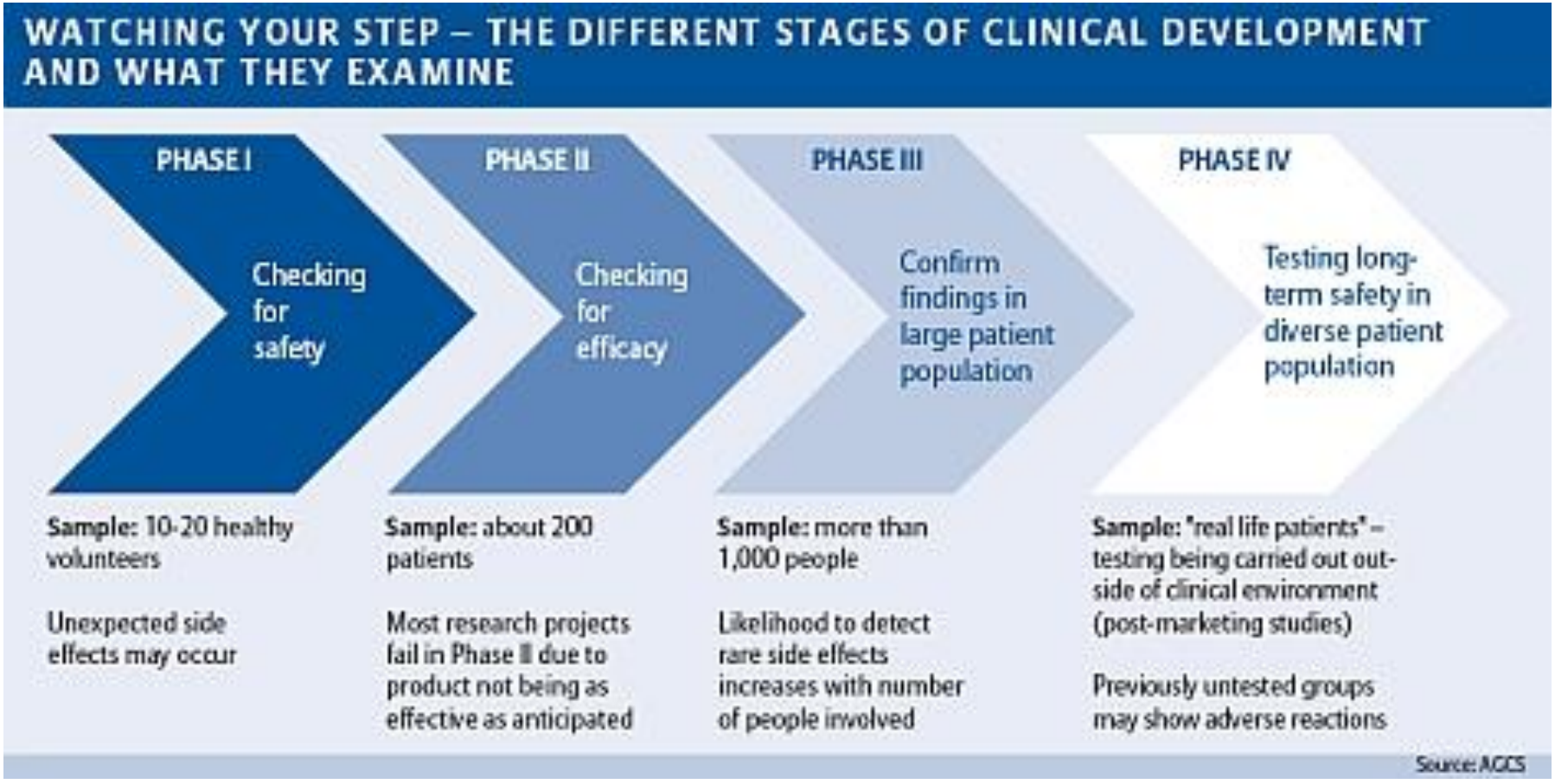
Note. For the PROMIS, BFI, and MFSI–SF: higher scores indicate greater fatigue. BFI = Brief Fatigue Inventory; MFSI-SF I = Multidimensional Fatigue Symptom Inventory-Short Form; BPI = Brief Pain Inventory; PSQI = Pittsburgh Sleep Quality Index; STAI = State Trait Anxiety Inventory; CESD = Center for Epidemiology Studies-Depression; PSS = Perceived Stress Scale; IL 1b = Interleukin-1b; TNF-α = Tumor necrosis factor-alpha.

- Fatigue one of the two most important outcomes (along with pain) in FDA public patient forum
- Correlated with total Hb
  - Ameringer S, Elswick RK Jr, Smith W. Fatigue in adolescents and young adults with sickle cell disease: biological and behavioral correlates and health-related quality of life. J Pediatr Oncol Nurs. 2014 Jan-Feb;31(1):6-17. doi 10.1177/1043454213514632. Epub 2013 Dec 30. PubMed PMID: 24378816; PubMed Central PMCID: PMC3982311.

Tentative List of SCD Clinical Trial Outcomes

- Hb (Hb F), Anemia
- WBC
- Pain
- Fatigue
- Utilization (No. Visits/Time, Length Of Stay)
- Acute Organ Damage
- Chronic Organ Failure

Usual Drug Development Steps

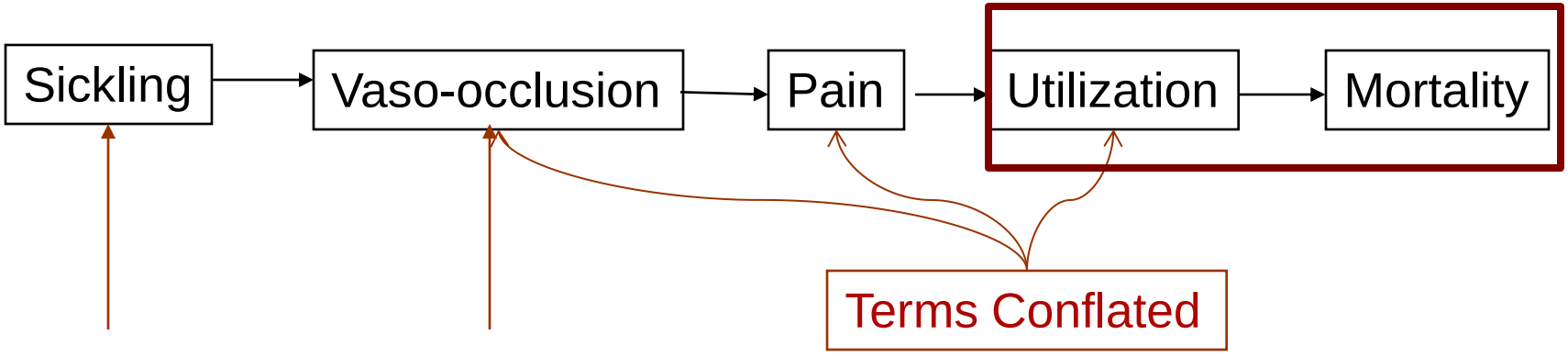


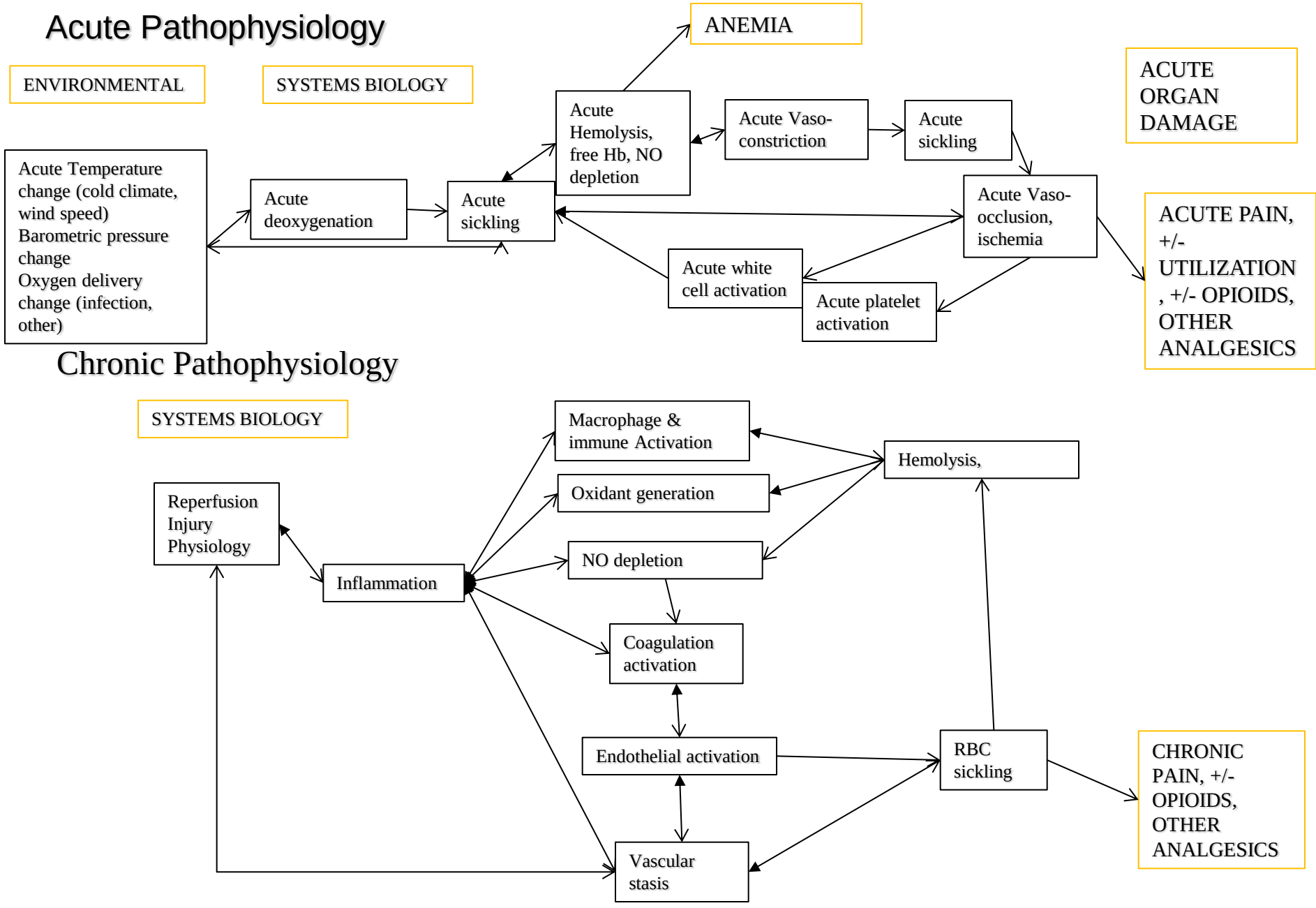
Sickle Cell Drug Development Steps

- Rare disease (100,000 in US)
  - Can't get thousands of patients for Phase III
  - Sometimes forced to combine steps of development
  - Not much "room" to experiment to determine appropriate outcome variables
- "Difficult to reach" patients
  - Minority, often poor, urban, underserved

CSSCD Results

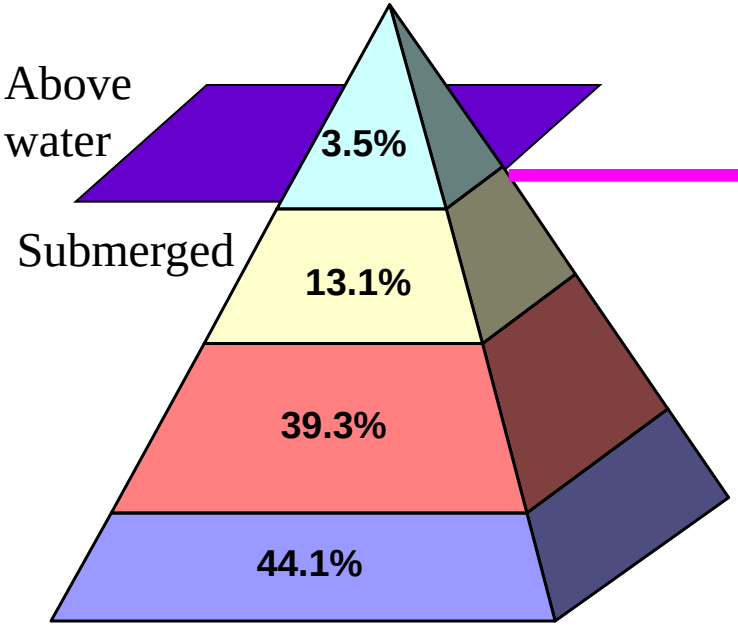
- Suggested simple model of attack
  - Model: Pain Equivalent to sickling, sickling equivalent to mortality
- Allowed for conflation of terms
- But 75 pts excluded because utilization was so frequent couldn't be counted easily





Acute inflammation, **Fig. (1). Probable hierarchy of the major sub-biologies participating in development of sickle vasculopathy. Modified from Kato GJ, Hebbel** RP, Steinberg MH, Gladwin MT; Vasculopathy in Sickle Cell Disease: Biology, pathophysiology, genetics, translational medicine and new research directions. [Meeting Report] *Am. J. Hematol.*, ***2009.***

Utilization is Rare, Crisis more common, and Pain VERY Common



Intensity	Mean	Std Dev
Utilization	**6.5**	**2.3**
Crisis w/o utilization	**5.5**	**2.1**
Pain w/o crisis, util.	**4.2**	**2**
No Pain	**0**	**0**

*Percentage of days. Utilization= utilization with or without crisis or pain; Crisis= crisis without utilization; Pain= pain without crisis or utilization

Adapted from Smith WR, et. al. Ann Intern Med 2008 Jan 15, 148(2):94-101

Crisis does not agree (kappa) with or well overlap with utilization

- DAYS
  - Utilization days coincided with crisis days (OR [95% CI]: 6.32 [5.57, 7.16]), but not beyond chance (Kappa = 0.1427).

• EPISODES*—Most crisis episodes are managed entirely at home.	Overlapped*		
	Yes	No	N
Crisis Episodes	21.4%	78.6%	1199
Utilization Episodes	62.1%	37.9%	462

* Episodes defined as contiguous days of either crisis or utilization. For crisis episodes, Overlapped = did utilization overlap? For utilization episodes, Overlapped = did crisis overlap?

Summary of Relationships Among Potential Outcome Variables

- CSSCD
  - Utilization rate over years neg. corr. survival
  - Utilization rate neg. corr. Hb F, pos. corr. total Hb (in Hb SS)
- PiSCES
  - Pain >>Crises>>Utilization (rare)
  - Pain intensity correlated with analgesic use (r=.83, p.>0001)
  - Pain intensity correlated with utilization (r=.50, p<.0001).
- MSH
  - The only remittive agent for SCD reduces utilization by half, prolongs life
  - But only minor (2.8-->2.5) statistically significant pain reduction (0-9 scale)
    - Smith WR, Ballas SK, McCarthy WF, Bauserman RL, Swerdlow PS, Steinberg MH,Waclawiw MA; Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. The association between hydroxyurea treatment and pain intensity, analgesic use, and utilization in ambulatory sickle cell anemia patients. Pain Med. 2011 May;12(5):697-705. doi: 10.1111/j.1526-4637.2011.01096.x. Epub 2011 Apr 11. PubMed PMID: 21481164.

Outcomes by Time Horizons

- Acute--Days to weeks
- Pain
- LOS
- Pain-related measures
- Crisis-related measures
- Opioid use (sparing)
- Example-Rivapansel phase II
- Subacute--months to a year
- “Severe” Crisis (utilization)?
    - Rare event
- Opioid use (sparing)
    - Controversial
- Hb, fatigue, Exercise capacity
- Examples: Hemaquest, SelG1, Sildenafil, Icagen
- Chronic—Years
- Utilization
- Organ Failure
- Examples MSH, CSSCD

Stages of Attack in Sickle Cell Disease

Disease Modifying			Palliative (analgesic)	
Acute	Chronic	Organ preserv	Acute	Chronic

- *Lopes BL, Flenders P, Davis-Moon L, Corbin T, Ballas SK. Clinically significant differences in the visual analog pain scale in acute vasoocclusive sickle cell crisis. Hemoglobin 2007;31(4):427-432.
- Todd KH, Funk KG, Funk JP, Bonacci R. Clinical significance of reported changes in pain severity. Ann Emerg Med 1996;4(4):485-489.

Endpoints in SCD: Summary

- Rare disease
- Multiorgan
- Multiple biologies awry
- Acute and chronic endpoints
- Approach to endpoints must keep all this in mind

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SPECIAL CONSIDERATIONS FOR ADULT CLINICAL TRIALS IN SICKLE CELL DISEASE

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October 9, 2014

Conflicts of Interest

- **Research funding from NK Therapeutics, Selexys Pharmaceuticals**
- **Consultant, scientific Advisory Board and honoraria from Pfizer, Selexys, Biogen Idec, Mast Therapeutics, Sangart**

Questions to be Addressed

- What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?
- For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease?
- Define further clinical benefit in the adult SCD patient
- What are the specific considerations for trial design and monitoring for adult patients with SCD?
- Are there any specific thoughts on the use of hydroxyurea during clinical trials that are studying a novel agent? Challenges and benefits?

Question

- **What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?**

What is considered the ideal trial design for adult patients with SCD?

- **Depends on specific SCD-related complication evaluated**
- **Clinical interventions in SCD may be classified as:**
  - **Prevention**
  - **Acute intervention**

Selected Acute Intervention Clinical Trials for Pain Crises

Intervention	# of Pts	Primary End Point	Study Findings	Reference
Cetiedil	67	Effect of cetiedil on course of pain crisis	↓ pain intensity; ↓ # of painful sites; ↓ duration of crisis; no diff. in doses of analgesics	Benjamin LJ et al, 1986
Methyl-prednisolone	36	Effect of methylprednisolone on duration & severity of pain crisis	↓ age-adj. duration of inpatient analgesic treatment; no diff. in ACS incidence; ↑ # of rebound pain episodes	Griffin TC et al, 1994
Purified poloxamer 188	255	Effect of PP-188 on duration of pain crisis	↓ duration of pain episodes - more pronounced ↓ in children and patients on HU. No diff. in secondary end points	Orringer EP et al, 2001
Inhaled NO	150	Effect of inhaled NO on duration of pain crisis	No diff. in median time to crisis resolution	Gladwin MT et al, 2011
Tinzaparin	253	Safety & efficacy of tinzaparin in pain crisis	Fewer total hospital days, overall days of crisis & days of most severe pain score	Qari MH et al, 2007
Arginine	38	Safety and efficacy of arginine in pain crisis	↓ in total parenteral opioid use and pain scores at d/c. No diff. in hospital LOS	Morris CM et al, 2013

Selected Prevention Trials for Pain Crises

Intervention	# of Pts	Clinical End Points	Study Findings	Reference
Ticlopidine	140	Effect of ticlopidine on pain crisis	↓ in # pain episodes; ↓ mean duration of pain episodes; ↓ severity of pain episodes	Cabannes R et al, 1984
Hydroxyurea	299	Efficacy of HU in ↓ frequency of painful crises in adult patients	↓ annual rates of pain crises; longer median times to 1st and 2nd crises; fewer episodes of ACS and RBC tx	Charache S et al, 1995
Senicapoc	289	Safety & efficacy of senicapoc in adult patients	No improvement in rate of pain crises; ↑ Hgb & Hct & ↓ dense RBC & retic count	Ataga KI et al, 2011
*Hydroxyurea	193	Effect of HU on splenic function and renal function	No sig. differences in splenic function or DTPA GFR; HU ↓ pain, dactylitis, ACS, hospitalization and transfusion; HU ↑ Hgb, HbF & ↓ WBC	Wang WC et al, 2011

Selected Trials for Other SCD-Related Complications

Intervention	# of Pts	Clinical End Points	Study Findings	Reference
Penicillin	215	Effect of PCN in ↓ incidence of documented septicemia due to S. pneumoniae	Sig ↓ incidence of infection in penicillin group	Gaston MH et al, 1986
Dexamethasone	38	Efficacy and safety of IV dexamethasone in mild or mod severe ACS	↓ hospital stay, clinical deterioration and need for blood tx; ↑ readmission in dexamethasone group	Bernini JC et al, 1998
RBC transfusion	130	Reduction of stroke in pts with ↑ risk by TCD	↓ 1st stroke in children with abnormal TCD with chronic transfusion	Adams RJ et al, 1998
Bosentan	26	1) Change from baseline in PVR at week; 2) change from baseline in 6MWD at week 16	Bosentan well tolerated; efficacy endpoints not assessed due to limited sample size	Barst RJ et al, 2010
Sildenafil	74	Change in exercise capacity (assessed by 6MWD) from baseline to week 6	↑ SAEs in sildenafil arm; no treatment effect on 6MWD, TRV or NT-proBNP	Machado RF et al, 2010

Question

- What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?
- **For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease? Are there other considerations for the study population? Are there certain stratification factors which are considered?**

For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease

- **Depends on SCD-related complication evaluated:**
  - **Painful crisis: e.g. # of medical contacts**
  - **Kidney disease: e.g. albuminuria**
- **Possible stratification factors:**
  - **Genotype - SS/Sβ^0 vs. SC/Sβ$^+$**
  - **Hydroxyurea use**
  - **Age**
  - **Complication - frequency of pain episodes, degree of albuminuria, etc**

Question

- What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?
- For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease?
- **Define further clinical benefit in the adult SCD patient**

Define further clinical benefit in the adult SCD patient

- **Definition of clinical benefit is not static**
  - **Depends on baseline state of disease severity in patient**

Question

- What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?
- For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease?
- Define further clinical benefit in the adult SCD patient
- **What are the specific considerations for trial design and monitoring for adult patients with SCD?**

What are the specific considerations for trial design and monitoring for adult patients?

- **Depends on clinical outcomes being evaluated**
  - **Pain crises – may not enroll patient with "infrequent" pain episodes (e.g. < 1 ED visit/year) in trial to evaluate decrease in pain frequency**

Question

- What is considered the ideal trial design for adult patients with sickle cell disease (SCD)?
- For chronic prevention, what is the baseline level of disease severity which should be considered to show a meaningful change in the disease?
- Define further clinical benefit in the adult SCD patient
- What are the specific considerations for trial design and monitoring for adult patients with SCD?
- **Are there any specific thoughts on the use of hydroxyurea during clinical trials that are studying a novel agent? Challenges and benefits?**

Are there any specific thoughts on the use of hydroxyurea during clinical trials that are studying a novel agent?

- **Hydroxyurea is "standard of care" for treatment of patients with severe SCA**
- **Challenges and benefits**
  - **May be more difficult to accrue subjects**
  - **May be concern for overlapping toxicities**
  - **Possibility of additive or synergistic effects with combination with new drug**

Thank you!

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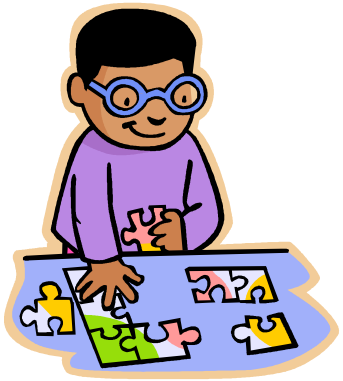

Special Considerations for Pediatric SCD Clinical Trials

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Disclosures

- Consultant Agreements with Pfizer, Lilly, Baxter, AstraZeneca, Biogen Idec, GlycoMimetics
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Pediatric Considerations

- Age-related
- Disease-related
- Organ function-related
- Ethical considerations
- Other issues

Age-Related Considerations

- Many not unique to SCD
- Large range of weight and size
  - Dosing considerations
  - Formulation considerations
  - Blood sampling restrictions
- PRO considerations
  - Age/cognitive ability
  - Proxy reporting
  - Pediatric versus adult measures

Disease-Related Considerations

- Some complications more frequent in pediatrics
  - Splenic sequestrations
- Other complications uncommon in pediatrics
  - Leg ulcers
- Age-related changes in complication frequency
  - ACS
  - Pain
- Age-related changes in characteristics of complications
  - Recurrent acute pain versus chronic pain

Disease-Related Considerations

- Antecedents of adult complications
- Preventable risk factors versus early onset
  - Frequent recurrent acute pain leading to chronic pain
  - Frequent ACS leading to chronic pulmonary disease
  - Avascular necrosis
  - Pulmonary hypertension
- Adolescents

Developmental/Disease Related Changes in Organ Function

- Splenic function lost at early age
- Accelerated renal clearance in childhood that declines with age
  - Drug exposure considerations
  - Impact on PK/PD
  - Age-related changes in toxicities?

Ethical Considerations-Impact on Design

- Prospect of direct benefit
- Placebos
- Parents providing permission for minor children
  - Risks versus benefit

Other Issues

- Increasingly widespread use of hydroxyurea in early childhood
  - Has this substantially changed pain frequency in young and school-aged children?
- Need for international studies?

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Patient-Reported Outcomes in Clinical Research for Sickle Cell Disease: An Overview

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Objective

- To provide an overview of, and review considerations for, the use of patient-reported outcomes in sickle cell disease related clinical research

Patient-Reported Outcomes (PROs)

- FDA Definition:

  "Any report coming directly from patients, without interpretation by physicians or others, about how they function or feel in relation to a health condition and its therapy" – (Patrick et al., 2007)

Examples of PROs

- Health Related Quality of Life (HRQoL)
- Health status (i.e., biological or physiological (dys)functioning
- Psychological Well-being (e.g., depression, anxiety, coping)
- Satisfaction – the subjective appraisal of a patient's experiences of treatment, including side effects, convenience, efficacy
- Symptoms & Functioning (e.g., fatigue, sleep quality, activities of daily living)

Generic vs. Disease-specific PRO Measures

- Generic PRO measures can be used among multiple and varying population groups, including healthy and/or chronically ill groups
  - Facilitates cross-group comparisons of the burdens of different disease-states
- Disease-specific PRO measures designed to assess burdens/experiences of particular importance or quality to patients with a certain condition
  - These measures typically more responsive to changes or differences w/in the specified population

Benefits/Rationale for PROs in Clinical Research

- Provides a more complete picture of the burden of disease / value of treatments
- May help distinguish the relative benefits/burdens of alternative treatments with similar clinical effects
- Facilitates interpretations of the impact of potential treatments that may be more meaningful to patients/families/clinicians

(Revicki et al., 2007)

PROs & Medical Product Labeling/Advertising

- Both the FDA & the European Medicines Agency (EMEA) are willing to consider information on PROs in product labeling & advertising
- The FDA requires the same standard of evidence to approve PRO claims as used for any labeling claim (FDA Guidance, 2009)

Selected Components for FDA PRO Labeling Claim Submissions

- Provide Rationale for desired endpoints of study
- Provide Rationale for selected PRO measure(s)
- Describe Development of PRO measure(s) (*must* include patient input into item generation)
- Provide Conceptual Framework for the PRO measure(s) (show how framework related to endpoints)
- Provide Evidence of acceptability of the measure's respondent burden

(Revicki et al., 2007; FDA Guidance, 2009)

Selected Components for FDA PRO Labeling Claim Submissions

- Describe all specific targeted labeling claims related to all measured endpoints (e.g. “Product X reduces problems with…”)
- Provide psychometric properties of the PRO measures (e.g., content/construct validity, reliability, responsiveness)
- Provide guidelines for score interpretations
- Provide well-defined minimally important differences in selected PRO measures

(Revicki et al., 2007; FDA Guidance, 2009)

PROs for Sickle Cell Disease

- The use of PROs in SCD research is growing, with measures of pain or HRQoL being among the most common used

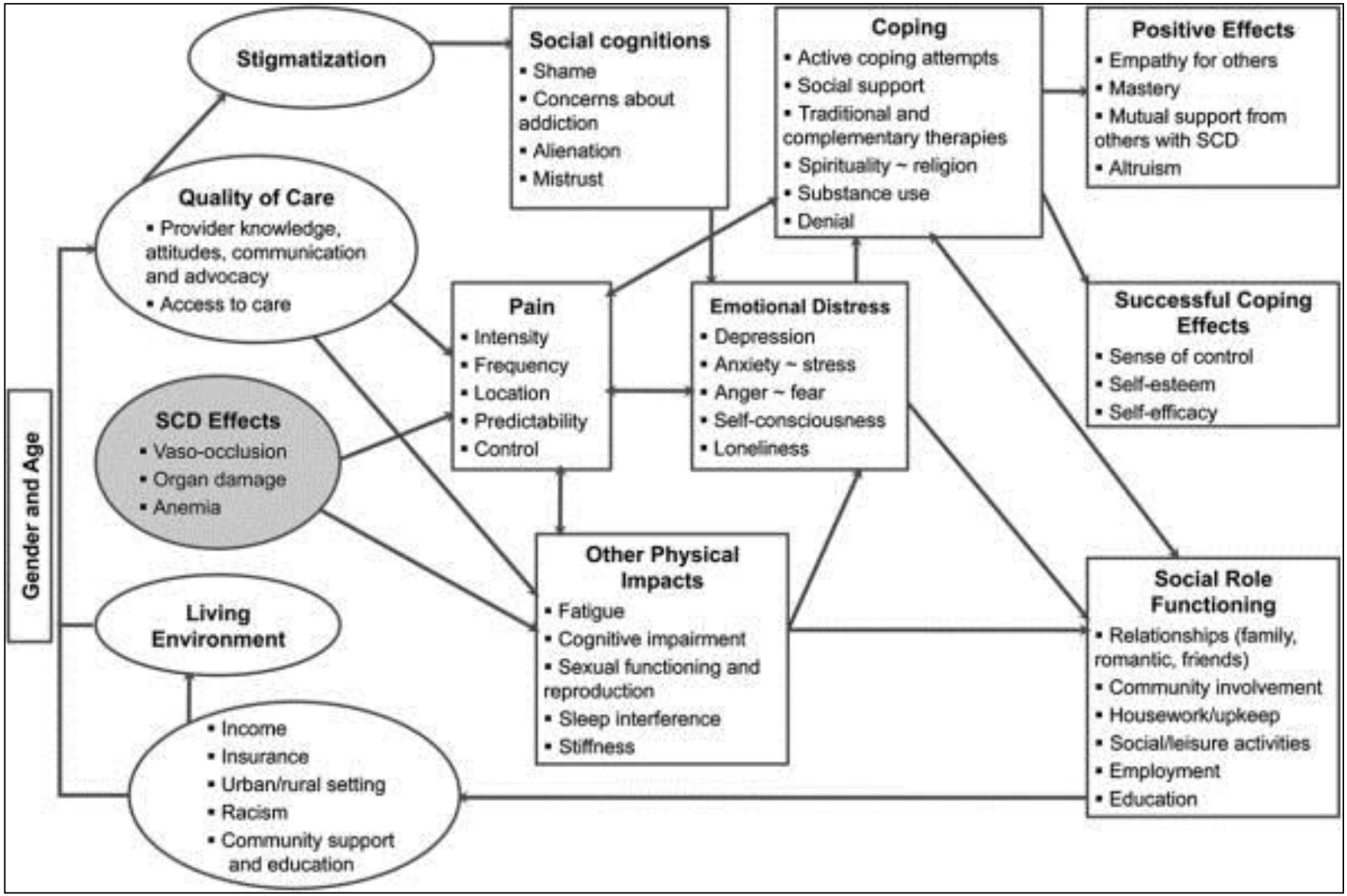
(Panepinto, 2012)

PROs for Sickle Cell Disease: Potential Domains to Target

- Pain & its Management
- Emotional Distress
- Social, Family, Work, & Sexual Functioning
- Quality of Life & Quality of Care

Treadwell et al. Adult Sickle Cell Quality-of-Life Measurement Information System (ASCQ-Me): Conceptual Model Based on Review of the Literature and Formative Research. Clinical Journal of Pain. 30(10):902-914, October 2014.

Conceptual Model: Impact of SCD on Adults



Treadwell et al. Adult Sickle Cell Quality-of-Life Measurement Information System (ASCQ-Me): Conceptual Model Based on Review of the Literature and Formative Research. Clinical Journal of Pain. 30(10):902-914, October 2014.

A Sampling of PRO Measures Used for Sickle Cell Disease

- Generic HRQoL Measures
  - PedsQL, Child Health Questionnaire, SF-36, SF-12
- Other Measures
  - HU therapy acceptance & adherence, Pain intensity, fatigue, activity interruption, analgesic use, energy level, experience of SCD-related complications, nature of sexual experiences

(Panepinto, 2012; clinicaltrials.gov)

New PRO Measures of SCD HRQoL

- Disease-specific
  - PedsQL-SCD module
  - Adult Sickle Cell Quality of Life Measurement Information System (ASCQ-Me)

(Panepinto, 2012; Keller et al., 2014)

Going forward in the use of PROs for SCD Research….

- Hopefully, greater testing of the PedsQL and ASCQ-Me will provide us with standard tools and outcome norms that will facilitate greater cohesiveness in our understanding of SCD patient experiences and the impact of standard and new therapies on those experiences

Going forward in the use of PROs for SCD Research….

- Is there a need for us as an SCD community to develop/establish a “standard PRO measure set” for use in research and clinical care?

- If so, how do we as an SCD community go forward in establishing/agreeing on this set?

- How do we encourage and facilitate the routine collection and use of this data in our clinical care?

Going forward in the use of PROs for SCD Research….

- I see this as a potential opportunity for us as a patient community to work with our clinicians and researchers to come to some sort of consensus/agreement…perhaps through a coordinated use of patient registries (for example)

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Suggested Readings

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