SICKLE CELL DISEASE SEVERITY: A NEW FIT-FOR-PURPOSE MEASURE OF TREATMENT IMPACT TO SUPPORT THE CLINICAL DEVELOPMENT OF GBT440, A NOVEL AND POTENTIALLY DISEASE MODIFYING THERAPY FOR SCD

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DISCLOSURES

• Laurie Burke is the Founder and CEO of LORA Group, LLC. She provides regulatory advice and is a principle investigator in multiple PRO measure development projects for biopharmaceutical companies.

• This SCD PRO research was funded by Global Blood Therapeutics, Inc., South San Francisco, CA.

• Employees of Global Blood Therapeutics:
  – Josh Lehrer-Graiwer, MPhil, MD, FACC
  – Ken Bridges, MD
  – Martine Kraus, PhD
  – Eleanor Ramos, MD
GOALS OF THIS PROJECT

- Identify outcomes (concepts) that are **meaningful and relevant to patients** and other healthcare decision-makers
- Define the context for use in future clinical trials
- Develop a measure that generates a score that is meaningful, interpretable, not misleading, useful and appropriate for the context of use
- Develop a measure that is
  - Sensitive to treatment impact, i.e., able to detect clinically meaningful improvement or worsening in response to an intervention
  - Consistent with the regulatory requirement for **well-defined and reliable** outcome assessments
  - Interpretable based on the recommendations found in the FDA PRO Guidance
  - Fit for purpose to assess clinical benefit for GBT440, a potentially disease modifying therapy for SCD
FDA DEFINITION OF “TREATMENT BENEFIT”

• Survival
• How patients feel or function in daily life
  – Symptoms
  – Difficulty with daily activities
• Impact of how patients feel or function in daily life on QOL

Optimally, treatment benefit is measured directly.
  – A surrogate or other indirect measure of treatment benefit may be useful IF the relationship between the indirect measure and treatment benefit is known
    o Ex: Hemoglobin
“FIT FOR PURPOSE” VS “VALIDATED”

- Tools are evaluated in the context of a proposed study.
- Validated/validation is not dichotomous (yes/no).
- Validation is the process of accumulating evidence to support the validity, reliability and sensitivity of the measure in a specific context.
- A “validated” instrument for all contexts does not exist.
Low in energy
Tired
Difficulty with concentration
Difficulty with daily activities
Pain intensity
Physical weakness
Breathing problems
Joint stiffness
Depressed mood
Sleep disturbance

SCD Severity Score
QUALITATIVE METHODS TO ESTABLISH CONTENT VALIDITY

- Protocol
- Interview guide
- Informed consent form
- IRB submission and approval
- Qualitative interviews
  - Concept elicitation using open-ended questions
  - Coding of transcripts and qualitative analysis
  - Sample size determined by evidence of saturation (i.e., no new information is spontaneously generated from additional interviews)
- Revision and drafting of content
  - Recall period
  - Response options
  - Finalization of scoring rule
  - Format (eDiary)
  - Instructions to patient
- Cognitive debriefing of final draft content
- Finalize and prepare user manual for investigators and patients
KEY QUALITATIVE ANALYSIS CONSIDERATIONS

- Degree of importance to the patient
- Relevance of the concept(s)
- Degree of difficulty to patient
- Degree of bother to patient
- Attribute to measure
- Patient language
- Degree of importance clinically and to measurement strategy
- Variability of occurrence
# Patient Characteristics (N=20)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of participants</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Female</td>
<td>16</td>
<td>80</td>
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<tr>
<td>Male</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>Age, years</td>
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<tr>
<td>Mean</td>
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<tr>
<td>18-29</td>
<td>6</td>
<td>30</td>
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<tr>
<td>30-59</td>
<td>14</td>
<td>70</td>
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<tr>
<td>Employment status</td>
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<tr>
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<tr>
<td>On disability</td>
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<tr>
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<tr>
<td>Post graduate degree</td>
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<td>10</td>
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<tr>
<td>Sickle cell genotype</td>
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<tr>
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<td>13</td>
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<tr>
<td>SBO</td>
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<td>SC</td>
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<td>Unknown</td>
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<td>15</td>
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<td>Crises requiring medical care in last year</td>
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</tr>
<tr>
<td>0</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>1-3</td>
<td>8</td>
<td>40</td>
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<tr>
<td>4 or more</td>
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<td>55</td>
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<tr>
<td>Pain medications</td>
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<tr>
<td>Opioids</td>
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<tr>
<td>Opioids + Morphine</td>
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<tr>
<td>Opioids + OTC</td>
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<td>Opioids + Prescription NSAIDs + OTC</td>
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<td>5</td>
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<td>Morphine</td>
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<tr>
<td>OTC analgesics</td>
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<td>Regularly scheduled blood transfusions</td>
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<tr>
<td>Hydroxyurea, currently using</td>
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INTERVIEW FINDINGS: “TYPICAL” PAIN

- Using a scale of 0 to 10 with 0 indicating no pain and 10 indicating worst imaginable pain, participants scored their typical pain as follows.
  - 0 (n=3)
  - 1-2 (n=1)
  - 3-4 (n=2)
  - 4-5 (n=3)
  - 5 (n=2)
  - 5-6 (n=3)
  - 6 (n=1)
  - 7 (n=1)

- The majority of participants (n=11, 55%) indicated that the typical pain was between 3 and 6 on the 0-10 scale.
“CRISIS” PAIN

- Using a scale of 0 to 10 with 0 indicating no pain and 10 indicating worst imaginable pain, participants scored their attack pain as follows.
  - 8 (n=1)
  - 8-9 (n=1)
  - 8-10 (n=2)
  - 10 (n=8)
  - 15 (n=1)
  - 20 (n=1)
  - 10+10+10 (n=1)
“CRISIS” PAIN

• Most participants (n=15, 75%) indicated that crisis pain is all throughout their body in contrast to their typical pain which was more localized. Some participants indicated that the attack pain may start in one area and then spread.

• The frequency of crisis pain varied across participants.
  – Twice a week (n=2)
  – Once a week (n=4)
  – Once every month (n=4)
  – Once every 2 months (n=2)
  – Once every 2-3 months (2)
  – 3-4 times a year (n=2)
  – 1-2 times a year (n=4)
PAIN LEVEL BEFORE SEEKING MEDICAL CARE

- 6-7 (to catch pain) (n=1)
- 7-10 (n=1)
- 8 (n=2)
- 8-9 (n=1)
- 8-10 (n=2)
- 9 (n=1)
- 10 (n=8)
- 10+ (n=2)

• All participants indicated that they took their strongest pain medicines and waited to see if the pain decreased before they sought medical care.

• Most participants reported that they delay going to the emergency department as long as they can because of the long waiting time in extreme pain as well as the under-treatment for pain they receive in the ER.
TIREDNESS AND FATIGUE

- Participants reported the following frequency of tiredness.
  - Every day, all the time (n=10)
  - 5 days/week (n=1)
  - 2-3 days/week (n=2)
  - 2 days/week (n=1)
  - 1-2 days/week (n=2)
  - 2 days/month (n=1)
  - 1 day/3 months (n=1)
  - Rare (n=1)
  - Never (n=1)
RELATIONSHIP BETWEEN TIREDNESS AND PAIN

- 8 participants reported that their pain and tiredness were not related to each other.
- 11 participants reported that these 2 symptoms were related
- 6 reported that pain increased their tiredness
- 3 reported that tiredness and fatigue led to pain and in some cases would lead to crisis pain.
EXPLORATORY QUANTITATIVE ANALYSES PLANNED WILL CONFIRM THE CONCEPTUAL FRAMEWORK

- This will support content validity, and define the final scoring rule
- New psychometric methods (e.g., Rasch Measurement Theory)
  - Endorsement frequencies
  - Item-person targeting
  - Response thresholds
  - Support for scoring algorithm and generation of subscales
- Classical test theory methods
  - Reliability (internal consistency)
  - Construct validity (convergent, discriminant, known groups)
NEXT STEPS

- Continue to generate qualitative data to test the draft conceptual framework of the new measure and finalize its content
  - Include all patient sub-populations that are relevant to future clinical trials
    - Adolescents
    - Other culture/language groups
- Demonstrate saturation and generate scoring rule
- Examine relationships--both cross-sectionally and longitudinally--between the new draft SCD severity score, patient characteristics and other outcomes
  - Age, sex, genotype, work status
  - Frequency of acute pain crises, blood transfusions, drug treatment
CONCLUSIONS

• A new SCD measure is needed to provide well-defined and reliable assessment of SCD severity

• It is anticipated that a patient-reported measure of daily patient experience will be more sensitive to signals of clinically meaningful treatment benefit that previous SCD outcome assessments (e.g., pain crisis episodes)

• An improved SCD endpoint measure may lower sample size requirements and thereby accelerate the development and approval processes for new SCD treatments such as GBT440