CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS Study Drug Log

Subject Name: _____ **CSCC ID#: _____** **Weight: _____**

Date of Next Study Visit: _____

		Check when dose has been taken.		
Day	**Day/Date***	**HU/Placebo Dose**	**Mg/Placebo AM Dose**	**Mg/Placebo PM Dose**
1	Wednesday, January 17, 2007			
2	Thursday, January 18, 2007			
3	Friday, January 19, 2007			
4	Saturday, January 20, 2007			
5	Sunday, January 21, 2007			
6	Monday, January 22, 2007			
7	Tuesday, January 23, 2007			
8	Wednesday, January 24, 2007			
9	Thursday, January 25, 2007			
10	Friday, January 26, 2007			
11	Saturday, January 27, 2007			
12	Sunday, January 28, 2007			
13	Monday, January 29, 2007			
14	Tuesday, January 30, 2007			
15	Wednesday, January 31, 2007			
16	Thursday, February 01, 2007			
17	Friday, February 02, 2007			
18	Saturday, February 03, 2007			
19	Sunday, February 04, 2007			
20	Monday, February 05, 2007			
21	Tuesday, February 06, 2007			
22	Wednesday, February 07, 2007			
23	Thursday, February 08, 2007			
24	Friday, February 09, 2007			
25	Saturday, February 10, 2007			
26	Sunday, February 11, 2007			
27	Monday, February 12, 2007			
28	Tuesday, February 13, 2007			
29	Wednesday, February 14, 2007			
30	Thursday, February 15, 2007			
31	Friday, February 16, 2007			
32	Saturday, February 17, 2007			
33	Sunday, February 18, 2007			
33	Monday, February 19, 2007			
33	Tuesday, February 20, 2007			
34	Wednesday, February 21, 2007			

HU/Placebo daily dose:
Mg/Placebo AM dose:
Mg/Placebo PM dose:

Reminders:

1) Do not break open HU/placebo capsules.

2) Study drug should be taken at (or close to) the same time each day.

3) Mg/Placebo doses should be taken about 12 hours apart.

4) If you miss a dose, just skip it and take the next scheduled dose.

5) All unused study drug should be returned to the CHAMPS Study Coordinator. This includes missed doses.

6) Rinse dosing syringes with hot water. Do not put dosing syringes in the dishwasher.

** Note to Study Coordinator - enter the date of the day after the study visit in Row 1, Column B of this spreadsheet in the DD/MM/YY format. All other days/dates will be adjusted accordingly.*

CHAMPS SUMMARY FOR HEMATOLOGY INPATIENT TEAM
January 2008

Study name: **CHAMPS** - Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hb SC Disease
Sponsor**:** NHLBI - Clinical Trial Consortium
Acronym**:** CHAMPS Accrual Goal: 35 local/ 188 study-wide
Eligible population**:** Age≥ 5 years; Hb SC; at least one VOC in past 12 months; no prior treatment with HU
Length of study participation**:** 12 months
Local PI**:** (include name, phone, pager)
Study coordinator**:** (include name, phone, pager)
Additional contact**:** (include name, phone, pager)

Study Goals:

1. To compare how hydroxyurea works alone, how magnesium pidolate works alone, and how hydroxyurea and magnesium work in combination in lowering the density of red blood cells.
2. To study how hydroxyurea and magnesium work alone and together in affecting hematologic measures, Hb F levels, other measures of red blood cell activity, and red cell activity, and red cell endothelial interactions, and how they may prevent vaso-occlusive episodes.
3. To study the safety of hydroxyurea and magnesium when used together.

Study Treatment: HU/Placebo 20 mg/kg/day capsules, Mg pidolate/Placebo 0.3 mEq/kg BID suspension

Stopping rules: Stop HU/Placebo and notify CHAMPS personnel if:

ANC < 1000/mm^3
Platelet count < 75 x 10^3/ mm^3
Hb ≥ 20% ↓ from Visit 1
Total Hb < 5 g/dL
SGPT > 2 x upper limit of normal
Cr ≥ 1.2 mg/dL (< 18 years old)
Cr ≥ 1.4 mg/dL (≥ 18 years old)

Stopping rules: Stop Mg/Placebo and notify CHAMPS personnel if:
Diarrhea Grade 3 or 4, diarrhea persisting more than 72 hours, signs of dehydration from diarrhea, or abdominal pain severe enough to interfere with ADL.

- Grade 3 is an increase of ≥ 7 stools/day OR incontinence OR IV fluids ≥ 24 hours OR hospitalization. Diarrhea does interfere with ADL.
- Grade 4 is life-threatening consequences.

Inpatient guidelines:

1. Study drugs only available through HOSP. Use home supply while inpatient.
2. Use caution when referring to study drug in documentation, some parents will report they are on HU or Mg when they mean study drug.
3. Care for acute events is unchanged from department standards. Routine care unchanged (PCN and Immunizations as per Heme recommendations).
4. ACS, splenic sequestration, stroke, sepsis, and osteomyelitis are serious adverse events which require FDA report (by study coordinator) within 24 hours of discovery
5. Study is open to enrollment. CHAMPS study brochure available to interested families.
6. Please contact CHAMPS Study Coordinator, NAME (PHONE) if family or in-patient team interested.
7. See intranet info for more details.

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CHAMPS Study Visit Calendar

Subject Name: _____ **CSCC ID#:** _____

Instructions: *Fill in the actual dates of Visits 1 and 2. Visit Windows will auto-fill based on the date of Visit 2. For Date of Visit 2: If the subject **does not** start study drug within a day of Visit 2, enter the date of the first dose of study drug.*

Visits with Central Labs (1, 2, 6, 8, 10 and 15) may NOT take place on a Friday; Monday through Wednesday preferred.

Date of Visit 1:	Monday, January 15, 2007
Date of Visit 2:*	Tuesday, January 23, 2007

**Reminder: If study drug is not started within a day of Visit 2, enter the date of the first dose of study drug.*

		Visit Window			
Visit #	**Week/ Timing of Visit**	**Earliest Date**	**Target**	**Latest Date**	**Actual Date of Visit**
Visit 3	Week 2 ± 4 days	Friday, February 02, 2007	February 6, 2007	Saturday, February 10, 2007	
Visit 4	Week 4 ± 4 days	Friday, February 16, 2007	February 20, 2007	Saturday, February 24, 2007	
Visit 5	Week 6 ± 4 days	Friday, March 02, 2007	March 6, 2007	Saturday, March 10, 2007	
Visit 6	Week 8 ± 4 days	Friday, March 16, 2007	March 20, 2007	Saturday, March 24, 2007	
Visit 7	Month 3 ± 8 days	Monday, April 09, 2007	April 17, 2007	Wednesday, April 25, 2007	
Visit 8	Month 4 ± 8 days	Monday, May 07, 2007	May 15, 2007	Wednesday, May 23, 2007	
Visit 9	Month 5 ± 8 days	Monday, June 04, 2007	June 12, 2007	Wednesday, June 20, 2007	
Visit 10	Month 6 ± 8 days	Monday, July 02, 2007	July 10, 2007	Wednesday, July 18, 2007	
Visit 11	Month 7 ± 8 days	Monday, July 30, 2007	August 7, 2007	Wednesday, August 15, 2007	
Visit 12	Month 8 ± 8 days	Monday, August 27, 2007	September 4, 2007	Wednesday, September 12, 2007	
Visit 13	Month 9 ± 8 days	Monday, September 24, 2007	October 2, 2007	Wednesday, October 10, 2007	
Visit 14	Month 10 ± 8 days	Monday, October 22, 2007	October 30, 2007	Wednesday, November 07, 2007	
Visit 15	Month 11 ± 8 days	Monday, November 19, 2007	November 27, 2007	Wednesday, December 05, 2007	
Visit 16	Month 12 ± 8 days	Monday, December 17, 2007	December 25, 2007	Wednesday, January 02, 2008	

Comprehensive Sickle Cell Centers Clinical Trials Consortium (CSCC CTC)
Statistics and Data Management Center
Checklist for Development of Informed Consent Materials for the Protocol:
Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial

Prior to and after submission to the investigator's IRB, the CSCC protocol committee for this study will review each site's informed consent/assent documents. Each site's informed consent document needs to include the following components:

1. _____ A statement that the study involves research.
2. _____ An explanation of the purposes of the study.
3. _____ The approximate number of volunteers to be involved in the study.
4. _____ A description of the procedures to be followed as well as identification and a specific description of any experimental procedures to be employed. Specifically, the volunteer will be subjected to blood draws, pregnancy tests (if applicable), an HIV-test, a clinical evaluation, and will be on one of four potential dosing regimens (placebo pill-placebo liquid, Hydroxyurea pill-placebo liquid, Magnesium pidolate liquid-placebo pill, Magnesium pidolate liquid-Hydroxyurea pill).
5. _____The expected duration of the volunteer's participation.
6. _____ A statement of the amount of blood (44 tsps.) to be drawn from the volunteer during the course of the study.
7. _____ A description of any reasonably foreseeable risks and discomforts to the patient or volunteers (includes ineffective treatment, if any). Serious risks identified in the protocol should be mentioned in the consent document. Listed potential risks must at a minimum include: decrease in blood counts, nail and skin pigmentation, reversible liver and kidney damage, cancer, diarrhea, and stomach pain caused by diarrhea.
8. _____ A description of the January 2006 Bristol-Meyers Squibb warning that HU may cause skin ulcers and gangrene, although no association has been seen with sickle cell patients.
9. _____ A statement of potential reproductive risk for women of childbearing age and demand the use of acceptable birth control. This section should include that a positive pregnancy test will be grounds for removing the person from the study.
10. _____A statement that Hydroxyurea and Magnesium Pidolate may involve currently unforeseeable risks to the volunteer, and that (at a minimum) the long-term risks of taking Hydroxyurea and Magnesium Pidolate are not known.
11. ____A statement that the volunteer will be notified of significant findings developed during the course of the research that may relate to the patient's or volunteer's willingness to continue participation in the study.
12. ____ A description of benefits to the volunteers or to others that may reasonably be expected from the study.
13. ____ No statements claiming any benefit for volunteers taking placebo.
14. ____ A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous or confer less risk to the volunteer (e.g. standard care).
15. ____ An explicit statement describing the extent, to which confidentiality of records identifying the volunteer will be maintained. The statement should note that i) the FDA, NHLBI, SDMC, (at a minimum) may inspect all medical records (including identification of the patient) when needed for the purpose of verifying the accuracy of data collection, ii) all of these parties are bound by the same requirements to maintain patient privacy that apply to all medical personnel, and iii) the volunteer will not be identified in any publication resulting from the

study.

16. ____ Listing of the CSCC Statistics and Data Management Center (SDMC; Rho) as a participating center (i.e. group/entity with rights to review research records and medical records).
17. ____ A statement that anonymized research records/data may be sent to places other than the investigator's office (e.g. to the SDMC at a minimum).
18. _____A description of what will be done with participants' data and research results upon withdrawal from or completion of the study
19. ____ A statement addressing additional costs to the volunteer resulting from participation in the study.
20. ____ A statement as to whether compensation or medical treatments are available if injury occurs, and, if so, what they consist of, or the persons to contact for further information.
21. ____The names of persons to contact for information or questions about: i) the volunteer's rights as a study participant, and ii) the study protocol. Included will be site-specific instructions about whom to contact in the event of a research-related injury to the volunteer.
22. ____ Explicit statements that the volunteer's participation is voluntary, that refusal will involve no penalty or loss of benefits to which the volunteer is otherwise entitled, and that the volunteer may discontinue participation at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. A statement indicating that the volunteer has not relinquished legal rights will be included here.
23. ____ A statement of what will be done with a volunteer subject's data following early withdrawal from the study.
24. ____ An explicit statement that the Principal Investigator, Sponsor (NHLBI) or the FDA (at a minimum) may stop the volunteer's participation in the study at any time, and some anticipated circumstances that might cause this to happen.
25. ____ All information concerning any direct compensation for time and inconvenience to the volunteer, including the maximum amount possible. May include itemized schedule of payments.
26. ____ Dated signatures of the Volunteer or Guardian, Investigator or authorized representative administering the consent, and a witness.

NOTE: THE NHLBI REQUESTS THAT PEDIATRIC SITES SUBMIT A CHILD ASSENT FORM AS PART OF THE IRB PACKAGE FOR THIS TRIAL. HOWEVER, IF A SITE'S IRB IS RESISTANT TO THIS, AND DOCUMENTATION OF THIS CAN BE PROVIDED TO NHLBI STAFF, THAT THIS REQUIREMENT CAN BE WAIVED.

HYDROXYUREA (AND PLACEBO) DOSING AND DOSE ADJUSTMENT TABLE

Dose and # of caps refer to both HU and Placebo

caps = number of capsules per day. If more than one number, the subject should take the first number on the first day, the second on the 2nd day, etc, and then repeat. E.g. if dose is 2/1/1: 2 pills on Day One, 1 pill on Day Two, 1 pill on Day Three, then repeat (2 pills on Day Four, 1 pill on Day Five, 1 pill on Day Six, repeat)

		20/mg/kg/d			17.5 mg/kg/d (1st Toxicity)			15 mg/kg/d (2nd Toxicity)			12.5 mg/kg/d (3rd Toxicity)		
Wt. (kg)	Wt. Range (kg)	HU/ Placebo Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)
15	12.6 - 17.5	300		2/1	262.5		2/1/1	225		2/1/1/1/1/1	187.5		1
20	17.6 - 22.5	400		2	350		2/2/2/1	300		2/1	250	1/0	
25	22.6 - 27.5	500	1		437.5		3/2/2/2	375		2	312.5		2/1
30	27.6 - 32.5	600		3	525	1		450		2	375		2
35	32.6 - 37.5	700	1	1	612.5		3	525	1		437.5		2
40	37.6 - 42.5	800		4	700	1	1	600		3	500	1	
45	42.6 - 47.5	900	1	2	787.5		4	675	1	1	562.5		3
50	47.6 - 52.5	1000	2		875		4	750	1	1	625		3
55	52.6 - 57.5	1100	1	3	962.5	1	2	825		4	687.5	1	1
60	57.6 - 62.5	1200	2	1	1050	2		900	1	2	750	1	1
65	62.6 - 67.5	1300	1	4	1137.5	1	3	975	2		812.5		4
70	67.6 - 72.5	1400	2	2	1225	2	1	1050	2		875	1	2
75	72.6 - 77.5	1500	3		1312.5	1	4	1125	1	3	937.5	1	2
80	77.6 - 82.5	1600	2	3	1400	2	2	1200	2	1	1000	2	
85	82.6 - 87.5	1700	3	1	1487.5	2	2	1275	1	4	1062	1	3
90	87.6 - 92.5	1800	2	4	1575	3		1350	2	2	1125	1	3
95	92.6 - 97.5	1900	3	2	1662.5	2	3	1425	2	2	1187.5	2	1
100	97.6 - 102.5	2000	4		1750	3	1	1500	3		1250	3/2	
105	102.6 - 107.5	2100	3	3	1837.5	2	4	1575	2	3	1312.5	1	4
110	107.6 - 112.5	2200	4	1	1925	3	2	1650	3	1	1375	2	2
115	112.6 - 117.5	2300	3	4	2012.5	4		1725	3	1	1437.5	2	2
120	117.6 - 122.5	2400	4	2	2100	3	3	1800	2	4	1500	3	
125	122.6 - 127.5	2500	5		2187.5	3	3	1875	3	2	1562.5	2	3

IRB Approval Process for Informed Consent Statements for the Hydroxyurea and Magnesium Pidolate for SC Patients Study (HU-Mg Study)

The informed consent statement describes in non-technical language the purpose of the study, the activities and procedures involved, the expected duration, the potential risks, benefits, and discomforts of participation, and alternatives to study participation. Each patient must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The table below shows the informed consent statement approval process. The CSCC Statistics and Data Management Center (SDMC) will track forms through this process; sites will not be allowed to enroll study subjects or controls until they have completed this process.

Site Consent Form Approval Process

Step	Action	Status
1	The HU-Mg Protocol Team develops an informed consent template	Completed
2	The template is reviewed and approved by the SDMC and Dr. Greg Evans at the NHLBI	Completed
3	A subcommittee of the Study PI, SDMC staff, and Dr. Evans develops a checklist that is used to review each site's consent forms to assure that the forms meet all regulatory requirements	Completed
4	Each site prepares a template-based consent form(s) for submission to its own IRB	

5	Using the checklist, the SDMC and NHLBI staff review the consent forms:
	• Forms will be returned to the site investigator for revision if they:
	  o do not satisfy the requirements on the checklist
	  o misstate a point (e.g., underplay a potential adverse event)
	• After forms are revised by the site, they are re-reviewed by SMDC staff	

6	Following approval from the SDMC, each site submits its consent forms to its own IRB	
7	IRB-approved consent forms are sent to the SDMC and reviewed as in Step 5, to assure that none of the key elements in the consents have been removed during the IRB review process: • Forms will be returned to the investigator for revision for the same reasons listed in Step 5 • When forms are resubmitted to the IRB, changes must be discussed with the IRB • If forms are acceptable, go to Step 8	
8	Notification that the consent forms contain the required elements, and that the site has obtained IRB approval of the forms is sent from the SDMC to the sites, and is forwarded to the DSMB and NHLBI	
9	The NHLBI approves the consent form(s)	
10	Each site keeps a copy of the original, approved consent forms and sends copies of all approved forms to the SDMC.	

Description of CHAMPS Lab Kits and Pharmacy Accessory Kits

Specimen Kits

Blood Sample Collection Kit: Each kit contains all items needed for one study visit for one subject, excluding the Shipping Kit. Each Blood Sample Collection Kit will be packaged in a plastic bag that is labeled with the protocol name, kit description, kit lot #, and expiration date of vacutainers. Study coordinators should always use the lab kit with the earliest expiration date.

- One 6-mL green vacutainer
- One 5-mL lavender vacutainer
- Two 10-mL lavender vacutainer
- Two 4-bay Aquipak (absorbent tube shuttle)
- Eight 12 x 12 ziplock bags (to contain ice)
- Two 6 x 9 ziplock bags (to contain plastic canister)
- Two FedEx airbill pouches

Refrigerated (Wet-Ice) Shipping Kit:

- One small foam cooler
- One cardboard box for small cooler
- One small canister (to place the 4-bay Aquipak enclosed in the 6 x 9 ziplock bag)
- One Biohazard label
- One UN3373 Diagnostic Specimens Label
- Two Up Arrow Labels
- One "LAB OPEN IMMEDIATELY CHAMPS STUDY"

Small 95 kPa Canister w/ Cap: These canisters are also part of the Refrigerated (Wet-Ice) Shipping Kit, but additional canisters may be ordered as canisters may crack or get lost in transit.

Pharmacy Accessories

Study Drug is ordered directly from UPM (HU/Placebo) or Xcelience (Mg/Placebo), but pharmacy supplies are ordered from Therapak.

- **Dosing Syringes** (5-mL, 10-mL, and 20-mL dispensers) – Dispense 4 dosing syringes with each monthly supply of Mg/Placebo
- **Mark-a-Dose Labels** – Used to mark the dose on each dosing syringe
- **Press-In Bottle Adapters** – 1 for each bottle of Mg/Placebo dispensed
- **7-day Pill Dispensers*** – Give each subject a 7-day pill dispenser with the first monthly supply of HU/Placebo, and ask him/her to bring it to each monthly visit so that it may be refilled. If the subject forgets, a new dispenser may be provided.

*If have a very small child who has experienced a Hydroxyurea/Placebo toxicity that requires complicated dosing, contact the SDMC study coordinator to request a supply of 30-day pill dispensers.

Pharmacy Accessories (continued)

Pharmacy Accessory Start-up Kit: A start-up kit may be ordered for the initial order. Please work closely with your site pharmacist to re-order materials as needed.

- ☐ 200 Mark-a-Dose Labels
- ☐ 50 5-mL Dispensers
- ☐ 100 10-mL Dispensers
- ☐ 50 20-mL Dispensers
- ☐ 40 Press-In Bottle Adapters

Items to Consider when Ordering Initial Supplies

- ☐ All orders must be made **at least one week prior** to needing the supplies.
- ☐ The number of subjects that can be potentially enrolled in the next 4 **week period**.
- ☐ As mentioned at previous study coordinator trainings and teleconference, the following **recruitment strategies** are recommended:
  1) Generate a list of eligible subjects (HbSC, at least 5 years of age, at least 1 vaso-occlusive event [pain or ACS] in the previous 12 months).
  2) Reinforce that this is the first major treatment trial for subjects with HbSC.
  3) Host a recruiting event.
  4) Utilize the recruiting brochure.
- ☐ Central labs are collected at Visits 1, 2, 6, 8, 10 and 15 (Week -1, Randomization, Month 2, Month 6, Month 8, Month 10, and Month 15).
- ☐ **Vacutainers have a 6-12 month life span**. Order conservatively to avoid having vacutainers expire before they are used.
- ☐ **The shippers take up space**. Order only as many as you can properly store in a safe place, where they will be used only for this study.
- ☐ **Order study supplies on an as-needed basis** as subjects progress through the study or as Blood Sample Collection Kits expire. Expiration dates are included on each kit.
- ☐ No more than 12 blood sample collection kits or refrigerated shipping kits may be ordered at one time. 12 kits are enough for 6 subjects to complete Visits 1 and 2, or for 3 subjects to complete Visits 1-9. This should allow ample time to re-order as needed.
- ☐ Contact Cathie Snyder at csnyder@rhoworld.com or (919) 408-8000 ext. 291 for one-on-one guidance in ordering supplies.
- ☐ Remember that the initial supply is to just get your site started. Supplies may be ordered whenever they are **needed**, but sites are asked to be conservative in an effort to minimize waste of supplies that are unused because of slow or no enrollment, subject ineligibility, and expiration of supplies.
- ☐ Dosing syringes (dispensers), Mark-a-Dose Labels, and Press-In Bottle Adapters will be stored in the pharmacy. Work closely with your site pharmacist to re-order as needed.
- ☐ The central labs will return the Styrofoam shippers to the sites, but the timeframe for return is not guaranteed.

Recommendation for Initial Order of Specimen Kits

1. Determine the approximate number of subjects that will be enrolled at the site during the next 4 weeks, and multiply by 6 (the number of visits with central labs). This is the total number of Blood Sample Collection Kits required for these subjects to complete the study.

2. Order enough lab kits for half of the subjects that will be approached/screened in the next 4 weeks, due to the expiration date and potential ineligibility/screen failures.

3. If there is not enough storage space to order per the recommendations above, order enough for all of the subjects to complete 2 visits. Central labs occur at Visits 1 and 2, and then not again until Visit 6 (which takes place at Month 2). This should allow ample time to re-order.

4. Re-order on an as needed basis, taking into account the dates of the next central lab visits, whether or not the subject is still enrolled in the study, etc.

Example based on a site that anticipates enrolling 4 subjects over the next 4 weeks:

4 potential subjects
x 6 visits with central labs
= 24 Blood Sample Collection Kits to complete the study

24 Kits
divided by 2
= 12 Blood Sample Collection Kits should be ordered to get started

Recommendation for Initial Order of Shipping Kits

Order enough shipping kits for all of the subjects that will be enrolled in the next 4 weeks to complete the first 2 visits. Since central labs occur at Visits 1 and 2, and then not again until Visit 6 (2 months after enrollment), there will be time to either receive the returned kits from the central lab or to re-order.

Example based on a site that anticipates enrolling 4 subjects over the next 4 weeks:

4 potential subjects
x 2 visits
= 8 shipping kits

CHAMPS MASTER PATIENT LIST

CSCC Study 6703

INVESTIGATOR:_____ Site: _____

Screening #	Screen Date	CSCC ID	Subject Name	Subject Address	Phone #	Phone #	Email Address
0001	*3/25/07*	*1234567*	*John Q. Public*	*345 Anywhere Street Anytown, Any State 12345*	*555-123-456*	*556-345-6789*	*JohnQ@whatever.com*

MAGNESIUM PIDOLATE (AND PLACEBO) DOSING & DOSE ADJUSTMENT TABLE

Wt. (kg)	Wt. Range (kg)	Initial Dose Mg Pidolate 0.3 mEq/kg BID		Dose after 1st Toxicity Mg Pidolate 0.225 mEq/kg BID		Dose after 2nd Toxicity Mg Pidolate 0.15 mEq/kg BID	
		(mEq)	(ml)	(mEq)	(ml)	(mEq)	(ml)
15	12.6 - 17.5	4.5	2.2	3.4	1.7	2.2	1.1
20	17.6 - 22.5	6.0	3.0	4.5	2.2	3.0	1.5
25	22.6 - 27.5	7.5	3.7	5.6	2.8	3.7	1.9
30	27.6 - 32.5	9.0	4.5	6.8	3.4	4.5	2.2
35	32.6 - 37.5	10.5	5.2	7.9	3.9	5.2	2.6
40	37.6 - 42.5	12.0	6.0	9.0	4.5	6.0	3.0
45	42.6 - 47.5	13.5	6.7	10.1	5.0	6.7	3.4
50	47.6 - 52.5	15.0	7.5	11.2	5.6	7.5	3.8
55	52.6 - 57.5	16.5	8.2	12.4	6.2	8.2	4.1
60	57.6 - 62.5	18.0	9.0	13.5	6.7	9.0	4.5
65	62.6 - 67.5	19.5	9.7	14.6	7.3	9.7	4.9
70	67.6 - 72.5	21.0	10.5	15.8	7.9	10.5	5.2
75	72.6 - 77.5	22.5	11.2	16.9	8.4	11.2	5.6
80	77.6 - 82.5	24.0	12.0	18.0	9.0	12.0	6.0
85	82.6 - 87.5	25.5	12.7	19.1	9.5	12.7	6.4
90	87.6 - 92.5	27.0	13.5	20.2	10.1	13.5	6.8
95	92.6 - 97.5	28.5	14.2	21.4	10.7	14.2	7.1
100	97.6 - 102.5	30.0	15.0	22.5	11.2	15.0	7.5
105	102.6 - 107.5	31.5	15.7	23.6	11.8	15.7	7.9
110	107.6 - 112.5	33.0	16.5	24.7	12.3	16.5	8.2
115	112.6 - 117.5	34.5	17.2	25.9	12.9	17.2	8.6
120	117.6 - 122.5	36.0	18.0	27.0	13.5	18.0	9.0
125	122.6 - 127.5	37.5	18.7	28.1	14.0	18.7	9.4

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

PREGNANCY FOLLOW-UP FORM

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

PREGNANCY STATUS (Check all that apply)

Pregnancy Ongoing	☐	Premature Delivery	☐	Spontaneous abortion[1]	☐	Ectopic Pregnancy	☐
Vaginal Delivery	☐	Stillbirth	☐	Threatened abortion[2]	☐	Unknown	☐
C-section	☐	Therapeutic abortion[3]	☐	Missed abortion[4]	☐	Other (Provide details below)	☐
Forceps	☐	Elective termination	☐				

1. Please submit an SAE form.
2. A threatened abortion is a condition of pregnancy, occurring before the 20th week of gestation, that suggests potential miscarriage may take place.
3. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred.
4. Therapeutic abortion is defined as the termination of pregnancy before fetal viability in order to preserve maternal health. (eMedicine.com)

RELEVANT LABORATORY TESTS/PROCEDURES PRE AND POST OUTCOME (e.g., Amniocentesis, ultrasound, MSAFP)

	Tests	Results Including units & normal values if applicable	Pending	Pre/Post Outcome?	Date DD/MMM/YYYY
1	_____	_____	☐	Pre ☐ Post ☐	_____
2	_____	_____	☐	Pre ☐ Post ☐	_____
3	_____	_____	☐	Pre ☐ Post ☐	_____

Further details: _____

_____

PREGNANCY OUTCOME

Infant/Fetal Outcome:

Unknown	☐	
Lost to follow-up	☐	
Number of infants/fetuses		(In the event of more than 1 infant/fetus, complete Infant Information section on a separate form for each infant/fetus.)
Normal baby	☐	
Normal fetus	☐	
Birth defect (structural/chromosomal)	☐	
Other disorder (non-structural, premature birth)	☐	
Death	☐	Date: _____ Cause of death:

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

Center code: | | | |

Hospital code: | | | |

PREGNANCY FOLLOW-UP FORM

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

CONCOMITANT MEDICATIONS

☐ No relevant concomitant medications

List relevant medications taken before and during pregnancy. If father exposed, enter medication taken prior to conception only..

Medication (generic name)	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Dose	Indication	Suspect
1.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
2.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
3.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
4.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
5.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No

INFANT INFORMATION

Infant/Fetal Outcome:

Gender	Weight:	Length:	Head Circumference:
Male ☐	_____ lbs	_____ inch	_____ inch
Female ☐	_____ kgs	_____ cm	_____ cm

Gestational Age at Delivery/Abortion _____ (weeks)

Apgar Scores 1 minute _____ 5 minutes _____ 10 minutes _____

HIV -1 Status: Negative ☐ Positive ☐ Unknown ☐

Were there any unusual features about the pregnancy or its outcome? Yes ☐ No ☐

If Yes, specify: _____

_____

_____

_____

Follow-up Examination of the Child:

Date:_____ Findings: _____

_____

_____

_____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

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PREGNANCY FOLLOW-UP FORM

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

RELEVANT LABORATORY TESTS/PROCEDURES FOR BABY/FETUS

	Tests	Results Including units & normal values if applicable	Pending	Date DD/MMM/YYYY
1			☐	
2			☐	
3			☐	
4			☐	

BIRTH DEFECT INFORMATION (Continue on Supplementary Form if necessary)

Were any birth defects noted? Yes ☐ No ☐ (If yes, complete information below.)

	Description of Birth Defect(s)	Attributable to ARV treatment? Y=Yes N=No U=Unknown	Other contributing factors: MA=Maternal Age U=Unknown O=Other
1			
2			
3			
4			

FETAL LOSS INFORMATION (Still birth, spontaneous, or abortion)

If a fetal loss occurred, were there factors, other than birth defects(s), that may have had an impact on the loss?
Yes ☐ No ☐ If yes, describe below.)

_____

_____

_____

ADDITIONAL INFORMATION (Continue on Supplementary Form if necessary)

_____

_____

_____

Signature: _____ Date of Signature: _____

Print Name: _____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

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PREGNANCY FOLLOW-UP FORM

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

SUPPLEMENTARY INFORMATION FORM FOR PREGNANCY FOLLOW-UP FORM

ADDITIONAL INFORMATION (Optional):

_____

_____

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Signature: _____ Date of Signature: _____

Print Name: _____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: ☐☐☐☐☐☐☐

Center code: ☐☐☐

Hospital code: ☐☐☐

PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

Subject's Date of Birth:_____ Subject's Weight: ___ ___ ___ lbs./ kgs. Subject's Gender: ☐ Male ☐ Female

STUDY DRUG INFORMATION

Study Product Name	Dose at Conception	Batch #	Time of Exposure			Start Date (DD/MMM/YYYY)	Stop Date (DD/MMM/YYYY)
			Preconception	Trimester	Delivery		
Hydroxyurea/ Placebo capsules (PO)	_____ mg _____ mg/kg/day		☐	☐ 1 ☐ 2 ☐ 3	☐		
Magnesium Pidolate/ Placebo (PO BID)	_____ mEq _____ mg/kg/day		☐	☐ 1 ☐ 2 ☐ 3	☐		

* Document the complete dosing schedule the subject has received in the event summary on p 2.

CONCOMITANT MEDICATIONS ☐ No relevant concomitant medications

List relevant medications taken before and during pregnancy. If father exposed, enter medication taken prior to conception only..

Medication (generic name)	Start Date DD/MMM/YYYY	Stop Date DD/MMM/YYYY	Dose	Indication	Suspect
1.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
2.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
3.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
4.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No
5.	___/_____/____	___/_____/____	☐ Unknown		☐ Yes ☐ No

PREGNANCY INFORMATION

LMP Date: ___/_____/____

Date of Last Negative Pregnancy Test: ___/_____/____

Estimated Date of Delivery: ___/_____/____

Was estimated date corrected based on ultrasound? (Based on LMP)

Yes ☐ No ☐ N/A ☐

If "Yes" provide corrected date of delivery: ___/_____/____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

CSCC Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CSCC ID: | | | | | | | |

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PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

MATERNAL MEDICAL HISTORY

Contraception (may choose more than one)				**Number of Previous**		**Risk Factors/ Medical History**	
None	☐	Condom	☐	Pregnancies	_____	Unknown	☐
Contraceptive Medication	☐	Surgical Sterilisation (Male)	☐	Therapeutic Abortions	_____	Alcohol	☐
Diaphragm	☐	(Female)	☐	Spontaneous Abortions	_____	**Allergies***	☐
IUD	☐	Withdrawal	☐	Stillbirth	_____	**Diabetes***	☐
Infertility (Male)	☐	Rhythm	☐	Deliveries	_____	**Infection***	☐
(Female)	☐	Unknown	☐	Babies born with defects*	_____	Smoking	☐
Spermicide	☐	Withdrawal	☐			Drug abuse	☐
						Other/Relevant History	☐

Details: For all * items above, please provide details including dates & outcome as applicable.

_____

_____

_____

_____

_____

Was there a family history of birth defects? Yes ☐ No ☐ N/A ☐ If yes, describe the defects below:

_____

_____

_____

PATERNAL INFORMATION

Was there a family history of birth defects? Yes ☐ No ☐ N/A ☐ If yes, describe the defects below:

_____

_____

_____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

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PREGNANCY NOTIFICATION FORM - Initial Report

"Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial"

Report Date (DD/MMM/YYYY) _____/_____/_____

PREGNANCY STATUS (Check all that apply)

Pregnancy Ongoing	☐	Premature Delivery	☐	Spontaneous abortion[1]	☐	Ectopic Pregnancy	☐
Vaginal Delivery	☐	Stillbirth	☐	Threatened abortion[2]	☐	Unknown	☐
C-section	☐	Therapeutic abortion[3]	☐	Missed abortion[4]	☐	Other (Provide details below)	☐
Forceps	☐	Elective termination	☐				

1. Please submit an SAE form.

2. A threatened abortion is a condition of pregnancy, occurring before the 20th week of gestation, that suggests potential miscarriage may take place.

3. A missed abortion is when the embryo or fetus has died, but a miscarriage has not yet occurred.

4. Therapeutic abortion: Therapeutic abortion is defined as the termination of pregnancy before fetal viability in order to preserve maternal health. (eMedicine.com)

Signature: _____ Date of Signature: _____

Print Name: _____

When complete, fax to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: (919) 287-3998. Then e-mail CHAMPS_SAE@RhoWorld.com noting that a Pregnancy Notification Form has been faxed; include the CSCC ID number.

Articles on this pill-swallowing technique:

Blount, R.L., Dahlquist, L.M., Baer, R.A., & Wuori, D. (1984). A brief, effective method for teaching children to swallow pills. Behaviour Therapy, 15, 381-387.

Dahlquist, L.M., & Blount, R.L. (1984). Teaching a six year-old girl to swallow pills. Journal of Behaviour Therapy and Experimental Psychiatry, 15, 171-173.

Dr. Danita Czyzewski, Dr. R. Duane Runyan, and Ms. Gretchen Browne authored this primer. They and Dr. Mark Kline, Professor of Pediatrics at Baylor and Texas Children's, welcome your comments, suggestions, and questions. Please feel free to contact us, or Nacy R. Calles, B.S.N., R.N., our Education and Study Coordinator, at the address and telephone and fax numbers listed below, or by e-mail.

Texas Children's Hospital
6621 Fannin St., MC1-4000
Houston, Texas 77030
713/770-1038
713/770-1281 – fax
jasalaza@msmail.is5.tch.tmc.edu

Roche

F. Hoffmann-La Roche Ltd
Basel, Switzerland

HIV Therapy in Children

A primer on pill swallowing

This video and accompanying brochure are intended to instruct medical caregivers in a technique to teach pill-swallowing to children. This technique relies on the behaviour modification principle of shaping. Shaping involves teaching a child to do a difficult task by starting with a simple task and moving to progressively more difficult tasks. In this case, the child starts with very small pills and moves to large pills. Using this technique should help children keep performance anxiety low and motivation high, both of which are important while learning pill-swallowing. Using this technique in the manner in which it is presented and with the children for whom it is intended, should result in children quite rapidly gaining skill and confidence in pill-swallowing.

Inclusion/Exclusion Criteria

Which children are good candidates for learning pill-swallowing with this technique?

- Children who have had no previous experience swallowing pills or have had success swallowing smaller pills.
- Children who generally cooperate with medications.
- Children who are motivated to learn a new skill.
- Children who are four years old or older (younger children can learn to swallow pills but may not be able to adhere to a strict protocol as consistently as is necessary).

Which children are not good candidates for learning pill-swallowing with this technique?

- Children who have had negative experience swallowing pills or trying to swallow pills.
- Children who protest any kind of medication, even good-tasting medication.
- Children who are very anxious about medications or new experiences in general.
- Children who have general oral-motor problems such as speech problems or refusal to eat certain food textures.
- Children who exhibit general behaviour problems (e.g., temper tantrums, disobedience towards authority).

If the child meets at least one of the exclusion criteria for this technique, it will be more difficult to teach the child pill-swallowing. In these instances, it is better not to attempt this technique. The training will likely be unsuccessful, making pill-swallowing more difficult in the future. Children who are excluded from this protocol may benefit from a different pill-swallowing technique designed to target their problem areas. This type of program can be designed by a behaviourally-oriented psychologist.

Characteristics of the Trainer

The trainer must be able to maintain emotional neutrality. Parents and health care providers with a close relationship to the child are not likely to be good trainers.

The trainer must not be seen as an authority figure by the child or have an authoritarian style. Authority figures may make the child anxious and anxiety can make the act of swallowing difficult. Coercive strategies are ultimately counterproductive because the child needs to be fully cooperative to learn this skill.

Setting for Learning to Swallow Pills

The situation should not be pressured. Ideally, the child should learn when there is not an immediate medical need to take pills (or at least not an immediate need known to the child). Learning to take pills and then practicing by taking daily (non-chewable) vitamin capsules is ideal.

There should be no time constraints for completion of the training, though the training sessions generally should not last longer than 30 minutes.

There should be no exciting activities that the child is anticipating immediately following the learning session, because this could distract the child from learning a new skill.

There should be no distractions in the training room (e.g., television, people walking in and out, etc.)

Teaching the Child

- Tell the child that he/she will learn a new skill. Remind the child of other skills he/she is likely to have learned – skipping, dressing or eating independently.
- Separate the child from parents to learn pill-swallowing. Have the parent show confidence in the child's ability (e.g., 'I can't wait to see you swallow pills'). If parents are overprotective or

anxious, do not let child see it (i.e., coach parents beforehand to just show enthusiasm).

- Use short commands and be repetitive.
  - 'Sit up straight.'
  - 'Keep your head straight.'
  - 'Put the pill on your tongue.'
  - 'Drink the water.'
- The trainer models the behaviour for the child with the smallest placebo.
- The trainer places the pill on his/her tongue and drinks water.
- The trainer shows the child that his/her mouth is empty and that the pill is swallowed.
- The child then practices the behaviour.
- The child places the pill on his/her tongue and drinks water. If the pill does go down, the trainer should praise the child for successful trials (e.g., stickers, money, tokens). If the pill does not go down, the trainer should say, 'That is okay. Keep drinking.' Other than saying 'Keep drinking.' The trainer should not give any reassurance or multiple commands. The trainer should be quiet to allow the child to calmly swallow water.
- After a success, the trainer should then move quickly to the next trial. The trainer tells the child 'Next pill,' never 'Bigger pill.' The child sees only one size placebo at a time.
- When the child successfully swallows the largest pill, have the child demonstrate a successful trial for parents. This models the behaviour for parents and increases generalisability of the behaviour to other settings.

When to terminate the trial

- If the child wants to remove medication from the mouth, the trainer should initially suggest 'keep drinking.'
- If the child persists in wanting to remove the medication, the trainer should allow the child to remove the medication from his or her mouth.
- The trainer should have the child end with a success on either a smaller pill or water, if necessary, and praise the child for his/her efforts.

Relapse Prevention

Having children do anything everyday can be a challenge. The child may be sick or just not want to swallow the medicine. Here are some strategies that are useful in minimising the possibility of nonadherence.

Consistency is key. Ideally, make pill-taking part of the everyday routine (i.e., a habit like brushing your teeth or washing your face). Within reason take the pills at the same time and in the same place everyday.

Do not bargain or bribe the child to take medication. Bargains or bribes will likely cause the child to take medicine to earn a reward, rather than because it is a habit, an expected part of growing up, or good for him.

Avoid power battles with medications. Do not threaten the child with punishment for not taking medication. Do not attempt to 'trick' the child into taking medication (e.g., do not mix in foods, etc.)

Once in a while a child who can take medications may refuse. If the child is allowed to not take the medications in that instance, the likelihood of future nonadherence increases. Further, depending on the medications, nonadherence for even one day can have a huge impact on the effectiveness of treatment. When the child refuses to take the medication, the world should stop for this child until he/she takes the medication. Specifically, the child should not move on to other activities and should have no diversions until the medication is taken. At times, this may be very inconvenient for the parent. However, if parents do this each time there is a refusal, the likelihood of future refusals greatly decreases. If nonadherence lasts for more than one dosage of medication, consultation with the medical team and referral to a behaviourally-oriented psychologist is recommended.

Medication Adherence for Children and Families
Guidelines for Assessment and Support

Before prescribing - make sure families are ready for Antiretroviral Therapy (ART)

- Ensure families are part of and agree with treatment decisions
- Assess family's **life-style, priorities, beliefs** about treatment and its potential impact
- Ask about **prior experiences** with medications. Build on past success; address existing/potential problems
- **Educate** family about disease processes, purpose of medications, and importance of medication schedule. Use one-on-one teaching, group classes, peer group education/support or a combination. **Use home visits to teach**
- **Repeat** information as many times as needed before starting ART. Use handouts that are written clearly and simply
- When problems are identified that make adherence unlikely, discuss the need to **defer/delay or change ART**

Prescribe ART Therapy - when families are ready

- Develop a **realistic**, simple as possible medication schedule that fits the family's daily activities
- Make it **visual**. Include doses and times. Use calendar pages, tables, clock faces, etc. Use **pictures of pills. Color-code everything** - medication bottles, marked syringes, calendar, clocks, etc.
- Prepare the family for **common administration problems** and strategies to make medication taste better - masking taste, pill crushing, gel caps. Teach pill swallowing. Children as young as 4 can learn
- Prepare family for **common side effects** and how to manage them. Many families stop treatment when faced with unexpected side effects
- Emphasize child's need for **ritual, consistency, and supervision**. Give medications at the same time, same place, same way each day
- Plan a **trial run** with a realistic schedule and "dummy" pills/liquid such as empty gel caps, juice
- If possible, arrange to **start first dose under supervision** in clinic
- Prepare family for the **challenge.** Adherence to ART can be difficult, but **it is possible** and you can provide support and help

For more information, visit the National Pediatric & Family HIV Resource Center web site at http://www.pedhivaids.org or E-mail: ortegaes@umdnj.edu or Call 1-800-362-0071

Other resources on treatment adherence and HIV available at http://www.MATEP.org

Assessing Medication Adherence

Make assessment part of <u>every</u> visit to identify and prevent adherence problems. Effective assessment builds on trust and good communication

- **Do not assume** a family understands the child's medications and regimen. Ask for the name, purpose, dose, and time of each medication. Tell family you will **ask about medications** and how they are managing at each visit and **then do it**
- **Give permission for honesty:** Start with "Many families have trouble sticking to the medication schedule with their children"
- Do NOT make family members feel guilty if they have failed "perfect" adherence. The **goals of assessment** are to identify problems, to provide support, and to help the family problem-solve. Give positive feedback
- Ask **specific,** but **open-ended questions** to get a description of how medicines are managed at home; *"Tell me about giving medicines this morning..."* **Use prompts;** *"How did you give the Viracept tablets?" "How did you know which medicines to give?"*
- Display posters of medications in office/clinic. Use these to aid assessment
- Assess **recent missed doses** by self-report. *"How have you been doing? Have you missed any doses today?...yesterday?...in the last 3 days?"*
- Ask about any difficulties/problems in managing medications, and **focus on identified issues.** *"Were you able to wake up early enough to take your medicines before school?"*
- Whenever possible, use home visits as part of adherence assessment
- Review prescription medications brought to clinic
- Use multiple methods for adherence assessment: self-report, refills, pill counts/bottle checks, diaries, etc.
- **Follow-up** a new regimen with a **phone call** and/or **home visit** in the first few days. That's when problems occur and many families will not call.

Other Strategies to Support Adherence

Regimen-Focused Strategies

- **Simplify** the regimen: d/c unnecessary drugs, use drug combinations, BID vs. TID
- Arrange for **home delivery**/mail-order pharmacy
- Use G-tube, change regimen, etc.

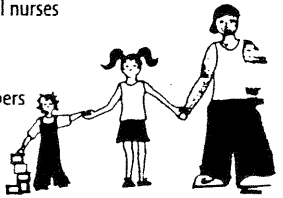
This educational material is supported in part by the HIV/AIDS Bureau, Health Resources and Services Administration, U.S. Department of Health and Human Services, project #6 U69 HA 00038-01

Child/Family-Focused Strategies

- Use individual and **group teaching**; peer **support**
- Employ anticipatory problem-solving: ***What to do for:*** vomiting; side effects, forgotten/missed doses, weekends, travel
- **Show families how meds are working.** A simple chart of rises in CD4 counts and falls in viral loads can be a positive reinforcement
- Foster family/youth **medication self-sufficiency** by having them make medication schedule, mark syringes, organize pill boxes, complete medication diary or adherence assessment tool
- **Involve children** in their medications and use **positive reinforcements.** Use realistic **incentives/rewards** to modify behavior
- Promote **developmentally appropriate** medication administration to children
- Utilize family/youth/school-age child **contracts**
- Consult a **Behavioral Psychologist** for help

Affective/Supportive Interventions

- **Case management** with a focus on adherence to therapies
- Family **meetings/peer groups**/individual counseling
- **Referrals** to support/correct medication administration/adherence. Educate these agencies on importance of adherence
- Visiting nurses, home health aids, school nurses
- Day care/after school programs
- Summer camp (child and/or family)
- **Disclosure** to child/and or family members
- **Substance abuse** counseling/treatment
- **Mental health** services



Provider-Focused Interventions

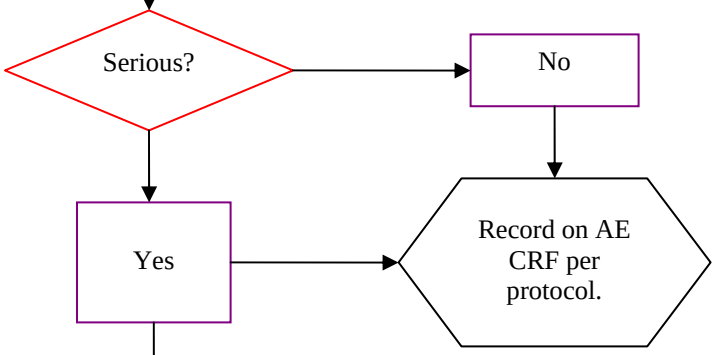
- Active listening, relationship building, improving **communication** skills
- **Commitment** to follow-up (telephone calls, home visits)
- Knowledge of **family's cultural context/beliefs** about medications
- A "system" for medication prescribing/adherence monitoring, including
  - **Structured** plans for starting ART
  - **Tools for assessing** adherence (reviewing prescriptions in clinic, refills, MEMs caps, pill counts, drug levels, self-report)

Other Supports

- **Family members, child life specialists, visiting nurses, social workers**
- **Pharmacists** as a key resource to review medication profiles, discuss potential interactions, provide medication consultation, reinforce instructions prior to dispensing

CHAMPS
SERIOUS ADVERSE EVENT (SAE) REPORTING FLOW

Subject Experiences an AE
(After informed Consent has been signed until 30 days after the last dose of study drug.)



Investigator/Study Coordinator at site:

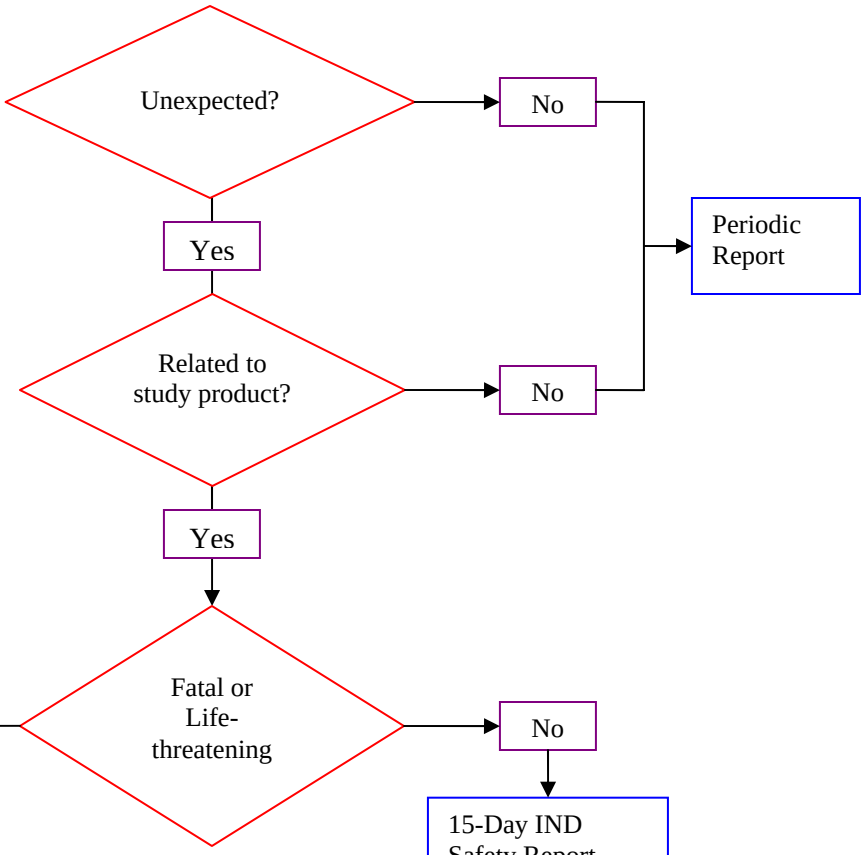
- Within 1 business day of the realization that an SAE has occurred in a study subject:
  - Complete the SAE Report form and fax to the attention of the
    CSCC SDMC SAE Regulatory Specialist
    (Product Safety Scientist),
    Rho Clinical Trials Safety Center
    (919)287-3998 or Toll Free: 888-746-3293
  - After faxing the SAE report, send an e-mail to Champs_SAE@RhoWorld.com noting that an SAE form has been faxed. Include the subject's CSCC ID number.

Day 0-2: CSCC SDMC SAE Regulatory Specialist (Product Safety Scientist):

- Within 1 business day, send an e-mail acknowledgement to the Investigator/Study Coordinator that the SAE was received.
- Performs the initial triage to determine regulatory reportability.
- Works with the site to ensure information is complete.
- Within 2 business days, drafts narrative of the event completes MedWatch form, if necessary.
- Sends the narrative, SAE Report, CSCC SAE Assessment Form, and all supporting documentation (SAE Packet) to the Medical Monitor.

Day 2-4: The Medical Monitor:

- Within 2 business days of receipt, reviews the SAE Packet and completes CSCC SAE Assessment form.
- Faxes Assessment form to CSCC SDMC SAE Regulatory Specialist (Product Safety Scientist).



Day 4-5 (No later than noon on Day 5)
CSCC SDMC SAE Regulatory Specialist (Product Safety Scientist):

- A fax will be prepared and submitted to Regulatory for initial notification to the Regulatory Authority.
- A complete MedWatch report will be submitted by Calendar day 15.

Day 10-12 (No later than noon on Day 12)
CSCC SDMC SAE Regulatory Specialist (Product Safety Scientist): Forwards Final MedWatch (3500A) to Rho Regulatory Affairs.

Rho Regulatory Affairs: By **Day 5** for 7-Day IND Safety Reports and by **Day 12** for 15-Day IND Safety Reports**,** prepares and forwards the Regulatory Packet to the Medical Officer.

Medical Officer: By **Day 6** for 7-Day IND Safety Reports and by **Day 13** for 15-Day IND Safety Reports**,** signs and forwards the Regulatory Packet back to Rho Regulatory Affairs.

By **Day 7** for 7-Day IND Safety Reports and by **Day 15** for 15-Day IND Safety Reports**:**

- **Rho Regulatory Affairs** submits the Regulatory packet to the FDA and notifies team that submission packet has been sent.
- **PI** submits DSMB report to the Chair of the DSMB subcommittee and to the NHLBI Project Officer. The PI is also responsible for submitting the SAE report to the investigators. SDMC study coordinator will assist in distribution of Dear Dr. letters.

Study Investigators:

- Submits SAE reports to the local IRB and other local authorities in accordance with the institution's regulations.

Follow-up reports are generated as necessary.

Instructions for Initial SAE Report

- SAE reporting is required for events that arise after the informed consent is signed until **30 days** after the last dose of study drug.
- All SAEs must be reported within **1 business day from when the site has become aware** of the event to the Lead P.I. and the CSCC SDMC SAE Regulatory Specialist.
- All site P.I.s are responsible for reporting SAEs to the appropriate IRB in accordance with their local laws and regulations.
- Complete and fax the SAE with any supporting documentation to the attention of the CSCC Clinical Safety Specialist, Rho Clinical Trials Safety Center at: **(919) 287-3998.**
- Then e-mail CHAMPS_SAE@RhoWorld.com noting that an SAE form has been faxed; include the CSCC ID number.

CSCC SAE Team:

1. Lead Principal Investigator: **Winfred Wang, MD**
2. Medical Monitor: **Ken Ataga, MD**
3. Rho, Inc. SDMC Lead: **Karen Kesler, PhD**
4. Rho, Inc. Study Coordinator: **Cathie Snyder**
5. Rho, Inc. Research Associate: **Emily Kunka**
6. Rho, Inc. SDMC SAE Regulatory Specialist (Product Safety Scientist): **Victoria C. Williams, PharmD**

General Instructions for SAE Reporting and Documentation

1. Complete all data fields (boxes) on the SAE form. The persons processing the form will not know if you left something blank intentionally (because the information is not available) or if you forgot to fill it in.
2. It is important to provide as much information as possible on the initial SAE report.
3. **If some information is not available at the time the initial SAE report is completed, at minimum, please provide the following information:**
   - CSCC ID
   - Center Code

- Hospital (Site) Code
- Site Name
- Report Date
- SAE Category
- Study Product Data
- Event Name
- Date of Onset
- Relationship of the event to the study drug

4. Write legibly staying within the boxes provided. If additional space is needed please use additional pages. Do not write in the margins, as this information may be lost when the form if faxed.
5. To delete or change an entry, use a black pen and draw a single line through the original entry. Initial and date the change.
6. Write "UNK" in the fields where information is not yet available. Please provide the missing information in the follow-up.
7. The date format is DD/MMM/YYYY (e.g.. 10/Feb/2006)

Instructions for Initial SAE Report

1. Check the **Initial Report** box located in the upper left corner, on all pages of the SAE report form.
2. Write the **CSCC ID**, **Center Code**, **Hospital Code**, **Site Name** and the **Report Date** on all pages of the SAE report form.
3. Write the **Subject's Date of Birth**.
4. Write the **Subject's Weight**. Circle the appropriate unit - **lbs. or kgs**.
5. Check the check box corresponding to the **Subject's Gender**.
6. **SAE category**: check all that apply.
7. **Study Product Data:**
    A. If the study product has not been started, write "not applicable" in the dose and date fields and indicate that study product has not been started in the "Other, specify" area of the ***Study Product Status*** field at the bottom left of page 1.

B. If the study product administration was complete before the SAE, write "not applicable" in the dose and date fields and check the "Study Product Administration Complete" check box in the ***Study Product Status*** field.

C. If the subject is on study product, indicate the time of the SAE and include the entire dosing schedule the subject had received in the Event Summary section of the SAE report form (including the taper given, if applicable):

D. **Dose, Route, Schedule of Study Product(s) at SAE Onset**: (Example of HU/Placebo: 700 mg per day; Example of Mg/Placebo: 6.7mL BID**)**

E. **Date Study Product Start Date**: the date the subject began the dose indicated in the ***Dose, Route, Schedule of Study Product(s) at SAE Onset*** field.

F. **Date Study Product Stop Date**: the date the subject stopped the dose indicated in the ***Dose, Route, Schedule of Study Product(s) at SAE Onset*** field. Select "Ongoing" if subject has not discontinued the dose.

8. **Event:** provide the diagnosis. Symptoms may be provided initially, but a diagnosis should be provided in follow-up. (e.g., Influenza instead of runny nose and fever).
9. **Date of Onset:** the date symptoms began.
10. **Severity:** check one box only.
11. **Relationship to Study Product: check ONE box only.**
12. **If NOT RELATED, is the event related to:** check the box(es) corresponding to the investigator's opinion of what the event is related to if "unrelated" was checked in the ***Relationship to Study Product*** field. Additionally, specify what the event is related to.
13. **Study Product Status:** For each study product, indicate if the administration of the treatment regimen was completed, continuing, deferred, adjusted, or whether a study product was discontinued permanently as a result of the SAE. If other course of action was utilized, please specify what that was. If the study product had not yet been started indicate in the "Other" check box that study product has not been started.
14. **Subject Status/Outcome:** If "Ongoing" is checked, the event must be followed until it is resolved or stable to a point that is acceptable to both the Investigator and the Medical Monitor. If the event outcome is "Resolved with sequelae," please list the sequelae (e.g., if

a subject were to experience a CVA with resulting left-sided weakness, the sequelae would be listed as left-sided weakness.)

15. **Event Summary:** please provide a complete description of the event, including any diagnostic or laboratory tests that were performed for diagnosis of the event. Also include intervention(s) provided for the event, course of the event, and outcome. Include any medical history that is relevant to the event. **Be sure to include the site number and the CSCC ID number on all supporting documentation. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)** Write the entire dosing schedule the subject has received (including the taper given if applicable) in the **Event Summary**.
16. **Laboratory Tests:** include relevant abnormal lab results that contribute to an understanding of the event. Provide normal ranges and previous lab results, which may be relevant to the event. **Please attach the lab reports to the SAE report form and indicate relevant results. Be sure to include the site number and the CSCC ID number on all lab reports. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)**
17. **Diagnostic Tests:** list relevant tests and test results for the event. **Please attach the diagnostic report to the SAE report form and indicate relevant results. Be sure to include the site number and the CSCC ID number on all diagnostic reports. Delete or completely obscure all personal information (name, subject initials, medical record number, etc.)**
18. **Concomitant medications:** list all relevant medications the subject was taking, starting from one month prior to SAE onset up to the time of SAE onset. Include the standard supportive care given to the patient (Analgesia, GI prophylaxis, and antimicrobial therapy). Enter the start date, stop date, dose, route, frequency, indication, and whether the medication was suspected in the causality of the SAE. If the medication was suspected in the causality of SAE, provide further detail in the event summary. If dose is unknown, check the unknown check box. If the subject was taking no relevant concomitant mediations, check the "No relevant concomitant medications" check box.

19. **Completed by/Investigator's signature:** the study staff member who completed the SAE form and the Investigator must sign and date the form.

Instructions for follow-up SAE Reports

1. Please complete a new CSCC SAE Report form promptly when new significant information is obtained regarding the SAE.
2. Complete the **CSCC ID**, **Center Code**, **Hospital Code**, **Site Name** and the **Report Date** on all pages of the SAE report form
3. Check the **Follow-up Report** box located in the upper left corner, on all pages of the SAE report form.
4. With the exception of the event and onset date, enter only information that is new or changed from the information previously submitted report. Include the event and onset date for reference.
5. The study staff member who completed the SAE form and the Investigator must sign and date the form.
6. Follow the SAE Reporting Guidelines listed under instructions for initial SAE report for directions on specific fields.

For questions about completing this form, please contact the CSCC Clinical Safety Specialist at (919) 408-8000 extension 237. Hours of availability are Monday-Friday, 8:30am-5:30pm, Eastern Time.

Contact Information:

CSCC SAE Regulatory Specialist
Rho Clinical Trials Safety Center
633 Quadrangle Drive, Suite 500
Chapel Hill, NC 27517
Phone: (919) 408-8000 x 237
Fax: (919) 287-3998

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS SCREENING / VISIT LOG
2 Pages per Subject; Visits 7-16 on Page 2

INVESTIGATOR:_____ SITE:_____

CSCC ID	Circle Gender	Screen Date	Screen Number	Screen Failure Reason	Protocol Version #	Visit 1 Week -1	Visit 2 Baseline	Visit 3 Week 2	Visit 4 Week 4	Visit 5 Week 6	Visit 6 Week 8	Unscheduled Toxicity Visit(s)
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											
	Male / Female											

Screen Failure Reason Codes

P-failure to meet % hyper-dense cells required
I – Inclusion criteria #____
E – Exclusion criteria #____

E-Term Drop Code

A = Adverse Event – specify event
N = Non-Compliance
P = Protocol Deviation
W = Withdrawal of consent
L = Lost to follow-up
O = Other – specify

All subjects who sign an Informed Consent Form must be included on this log

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS SCREENING / VISIT LOG
2 Pages per Subject; Visits 7-16 on Page 2

CSCC ID	Visit 7 Month 3	Visit 8 Month 4	Visit 9 Month 5	Visit 10 Month 6	Visit 11 Month 7	Visit 12 Month 8	Visit 13 Month 9	Visit 14 Month 10	Visit 15 Month 11	Visit 16 Month 12 (or Early Term Visit)	Unscheduled Toxicity Visit(s)

Screen Failure Reason Codes

P-failure to meet % hyper-dense cells required
I – Inclusion criteria #____
E – Exclusion criteria #____

E-Term Drop Code

A = Adverse Event – specify event
N = Non-Compliance
P = Protocol Deviation
W = Withdrawal of consent
L = Lost to follow-up
O = Other – specify

All subjects who sign an Informed Consent Form must be included on this log

CHAMPS PROTOCOL:
STUDY PERSONNEL SIGNATURE LOG/RESPONSIBILITY LIST

Site Name: _____ **Site Contact:** _____

Completion Instructions: All site personnel with responsibilities in this trial must be added to this form. Changes include additions/deletions to the site staff or changes in the responsibilities of existing staff. More than one person may be responsible for a given task. When completing this form, follow the example provided on the first row of the form. Additional copies of this form may be downloaded from the CHAMPS page of the CSCC website.

PRINTED NAME	TITLE	STUDY RESPONSIBILITIES	SIGNATURE	INITIALS	START DATE	END DATE
Jane A. Coordinator, RN	Study Coordinator	1, 2, 4, 7, 8, 10, 12	*Jane A. Coordinator, RN*	J.A.C.	10Mar2002	

*Record changes as the study progresses.

Study Responsibilities: **1**-Obtain informed consent, **2**-Obtain medical history, **3**-Perform physical exams, **4**-Inclusion/exclusion assessment, **5**-Drug dispensing, **6**-Drug accountability, **7**-Ongoing AE/con meds assessment, **8**-CRF completion, **9**-CRF signature, **10**-Query completion, **11**-Query signature, **12**- Update/maintain IRB docs, **13**-Other_____, **14**-Other_____.

CHAMPS PROTOCOL

STUDY PERSONNEL SIGNATURE LOG/RESPONSIBILITY LIST

PRINTED NAME	TITLE	STUDY RESPONSIBILITIES	SIGNATURE	INITIALS	START DATE	END DATE
Jamie A. Coordinator, RN	Study Coordinator	1, 2, 4, 7, 8, 10, 12	*Jamie A. Coordinator, RN*	J.A.C.	10Mar2002	

*Record changes as the study progresses.

Study Responsibilities: **1**-Obtain informed consent, **2**-Obtain medical history, **3**-Perform physical exams, **4**-Inclusion/exclusion assessment, **5**-Drug dispensing, **6**-Drug accountability, **7**-Ongoing AE/con meds assessment, **8**-CRF completion, **9**-CRF signature, **10**-Query completion, **11**-Query signature, **12**- Update/maintain IRB docs, **13**-Other_____, **14**-Other_____.

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Specimen Collection and Shipping to the Boston Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 6-mL green-top vacutainer and collect blood into the vacutainer *until it is almost full*. Do NOT remove the rubber top of the vacutainer.
2. Insert the needle into the rubber top of EACH of the 10-mL purple-top vacutainers and collect blood approximately half way into the vacutainer. Do NOT remove the rubber top of the vacutainer.
3. Place one barcode label on each of the three vacutainers, place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
4. Log into RhoLAB, select the correct subject ID, and add the barcode numbers on each of the 3 vacutainers into the system via the barcode scanner (this will be done simultaneously with the 5-mL lavender vacutainer going to the Duke lab).
5. Create a shipment within RhoLAB for all three vacutainers going to Boston (Brugnara) and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
6. Insert each of the three vacutainers into one Aqui-Pak absorbent pouch.
7. Roll up the Aqui-Pak tube-over-tube and insert it into the small 95 kPa canister.
8. Place the small 95 kPa canister into Biohazard plastic bag and place it upright inside the foam cooler.
9. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
10. Repeat Step 9.
11. Place the two bags of ice around the small 95 kPa canister.
12. Seal the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
13. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Boston (Brugnara) lab as the recipient of the 3 vacutainers.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
14. Place the return label on top of the foam cooler.
15. Tape the outer cardboard box shut.
16. Apply the "UN3373 Biological Substance" label to outside of box.
17. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
18. Apply the "biohazard" label to outside of box.
19. Apply the "LAB OPEN IMMEDIATELY HU-MG STUDY" label to the outside of the box.
20. Attach completed air bill to the outside of the box and send to the shipping area.

Carlo Brugnara, MD
Children's Hospital Boston
Department of Laboratory Medicine
300 Longwood Avenue, BA 766
Boston, MA 02115, USA
Phone: 617.355.6610
Fax: 617.730.0383
Email: Carlo.Brugnara@childrens.harvard.edu
Email (Lab Assistant): Corey.Hoehn@childrens.harvard.edu

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Specimen Collection and Shipping to the Duke Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 5-mL lavender-top vacutainer; collect blood into the vacutainer *until it is full*. Do NOT remove the rubber top of the vacutainer.
2. Place one barcode label on the vacutainer and place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
3. Log into RhoLAB, select the correct subject ID, and enter the barcode number on the vacutainer into the system via the barcode scanner.
4. Create a shipment within RhoLAB for the single vacutainer going to Duke and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
5. Insert the vacutainer into the Aqui-Pak absorbent pouch.
6. Roll up the Aqui-Pak and insert it into the small 95 kPa canister.
7. Place the small 95 kPa canister into the "Biohazard" ziplock bag and place it upright inside the foam cooler.
8. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
9. Repeat Step 8.
10. Place the two bags of ice around the small, bagged 95 kPa canister.
11. Close the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
12. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Duke lab as the recipient of the 1 5-mL lavender-top vacutainer.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
13. Place the return label on top of the foam cooler.
14. Tape the outer cardboard box shut.
15. Apply the "UN3373 Biological Substance" label to outside of box.
16. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
17. Apply "biohazard" label to outside of box.
18. Apply "LAB OPEN IMMEDIATELY CHAMPS STUDY" label to the outside of the box.
19. Attach completed air bill to the top of the outside of the box and send to shipping area.

Mardee Delahunty, MD
Duke University Medical Center
Research Drive
Room 337 MSRB
Durham, NC 27710
Phone: (919) 684-5999
Fax: n/a
Email: mardee@duke.edu
Email (Lab Assistant): katherine.sebastian@notes.duke.edu

Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS STUDY DRUG ORDER FORM:

Hydroxyurea and Hydroxyurea Placebo

Send completed Order Form to:
Attn: Carl Garnett
UPM
Fax: (410) 633-4438, or
E-mail: Garnett@upm-inc.com
Connell@upm-inc.com

Investigator: _____

Site Name: _____

Pharmacist: _____

Phone #: _____

Fax #: _____

# of Subjects (n/a for initial order)	**Current Inventory** (n/a for initial order)	**Product Name**	**Capsules per Bottle**	**# of Bottles Requested**
		Hydroxyurea 200 mg capsules	500	
		Placebo for Hydroxyurea 200 mg capsules	500	
		Hydroxyurea 500 mg capsules	500	
		Placebo for Hydroxyurea 500 mg capsules	500	

Pharmacy Shipping Address:

_____
Pharmacist Signature

_____
Date

_____
Requested Receipt Date

Instructions:

1) Type or clearly print all information.
2) Fill in all sections completely.
3) Sign and date order.
4) Enter requested receipt date.

Notes:

1) Study drug will only be shipped Monday-Thursday.
2) All shipments will be sent via Priority Overnight.
3) You will receive a notification from the RhoRAND system when study drug has been shipped.
4) Questions or problems with the Hydroxyurea/Placebo? Call John Connell at 410-843-3754.

Comprehensive Sickle Cell Centers Clinical Trials Consortium

CHAMPS STUDY DRUG ORDER FORM:

Magnesium Pidolate and Magnesium Pidolate Placebo

Send completed Order Form to:
Attn: Cathy Curtis
Xcelience
Fax: (813) 286-1105, or
E-mail: Cathy.Curtis@xcelience.com and
Irene.LoJacono@xcelience.com

Investigator: _____

Site Name: _____

Pharmacist: _____

Phone #: _____

Fax #: _____

# of Subjects (n/a for initial order)	**Current Inventory** (n/a for initial order)	**Product Name**	**Size**	**# of Bottles Requested**
		MagnesiumPidolate	480 mL	
		Magnesium Pidolate Placebo	480 mL	

Pharmacy Shipping Address:

Pharmacist Signature

Date

Requested Receipt Date

Instructions:

1) Type or clearly print all information.
2) Fill in all sections completely.
3) Sign and date order.
4) Enter requested receipt date.

Notes:

1) Study drug will only be shipped Monday-Thursday.
2) All shipments will be sent via Priority Overnight.
3) You will receive a notification from the RhoRAND system when study drug has been shipped.
4) Questions or problems with the Magnesium/Placebo? Call Cathy Curtis at 813-637-6042.

Study Start-up Materials
Regulatory Document Submission Instructions

Documents that must be submitted prior to site study initiation

- ❑ FDA Form 1572 (instructions for completing the form are provided below)
- ❑ For each PI and Sub-I listed in Item #6 on the 1572 form:
  - CV (no more than one year old); signed and dated
  - Copies of current professional license(s) (with expiration dates)
- ❑ For each PI and Sub-I listed in Item #6 on the 1572 form:
  - Financial Disclosure Form (original signatures)
  - Training documentation: Examples of acceptable documentation include rosters from training sessions, copy of a completion certificate or a note from the training group. The NIH offers free online training at http://cme.nci.nih.gov/ that provides documentation via certificate.
- ❑ Laboratory certification(s) (CLIA preferred).
- ❑ Laboratory normal ranges for CBC with reticulocyte counts, all chemistry labs listed in the protocol, and U/A. Include lab name (or other identifier linking the ranges to the laboratory) and version date.
- ❑ Protocol Signature Page: signed and dated original(s).
- ❑ IRB Approval Documentation: The IRB approval letter must identify the principal investigator or sub-investigator by name and reference all approved documents (protocol, informed consent, advertisements if applicable), including version numbers and version dates.
- ❑ IRB Compliance Documentation: FWA # and IRB roster if available. If a roster is not available, you will need to provide a statement from the IRB of CFR compliance.
- ❑ IRB Approved ICF's and advertisements if applicable.

Please Federal Express these materials as a complete packet, or as complete as possible. Note that IRB approval documentation may be submitted separately, and may be submitted via hard copy, fax, or e-mail (as a PDF document).

All regulatory documents should be submitted to:

Holly Forde
Rho, Inc.
6330 Quadrangle Drive, Ste. 500
Chapel Hill, NC 27517
Holly_Forde@rhoworld.com
fax (919) 287-3291

If you have questions, please contact Holly at (919)408-8000 ext. 207.

Instructions for completing FDA Form 1572:

Study Start-up Materials
Regulatory Document Submission Instructions

- Box 1: Name of PI with degree of PI listed.

  The PI's name is to be complete and spelled correctly, as verified by the information provided on the Investigator's curriculum vitae and license. The PI is not required to be an M.D. However, if the PI is not an M.D., at least one Sub-Investigator listed in Box 6 must have those credentials.

- Box 2: Either "CV" or "Other Statement of Qualifications" is checked.

  If "CV" is checked, a complete curriculum vitae is also to be included in the regulatory packet. If "Other Statement of Qualifications" is checked, information regarding the PI's credentials and qualifications are to be included in the regulatory packet.

- Box 3: Name(s) and address(es) of all study site(s) where subjects will be seen (no P.O. Box allowed without a street address). If the address is the same as in Box 1, please retype the address completely.

- Box 4: Name and address(es) of central and/or local lab (no P.O. Box allowed).

  A site may use their local laboratory and/or a central lab, as required by the protocol. If more than one lab is used in the conduct of a trial, *each* complete address (including the correct zip code) must be listed in Box 4.

- Box 5: Name and address of IRB is provided (no P.O. Box allowed).

  If a site is using more than one local IRB, the complete address (including correct zip code) for *each* IRB must be listed in Box 5.

- Box 6: Name of Sub-Investigator(s) provided with degree(s) of Sub-I(s) listed.

  If there are no Sub-I(s), the 1572 should state "None". There is no limit to the number of Sub-Is that may be listed in Box 6. If the list of Sub-Is exceeds the space provided in Box 6, an attachment to the FDA 1572 can be used. The names should match the names as presented on the CVs and medical licensure.

- Box 7: Full Name of the protocol (pre-populated).

- Box 8: Appropriate box checked (Phase II/III trials).

- Box 9: Section is pre-populated by FDA; no changes are allowed.

- Box 10 & 11: Signed and dated by PI.

  Box 10 must contain an original, handwritten signature. No stamped or photocopied signatures are allowed. The FDA 1572 must be dated on or after the final version of the protocol/protocol amendment.

CHAMPS Study Set-up Checklist for Sites

Getting Started

- ❑ Consent forms drafted and submitted to the SDMC
- ❑ Consent forms approved by the NHLBI for IRB submission
- ❑ Submit for local IRB review. Resubmit consents to the SDMC if changes requested by your site IRB.
- ❑ Submit a completed FDA Form 1572 and regulatory submitted to the SDMC, along with:
  - o CV and professional license for each PI and Sub-I listed
  - o Financial Disclosure Forms
  - o Laboratory certification(s)
  - o Training documentation for PI and each Sub-I on the Protection of Human Subjects in Research
  - o IRB Compliance Documentation (FWA # & IRB roster if available)
- ❑ Ensure that your local site pharmacist receives study training

When your site receives IRB approval

- ❑ Notify the SDMC that you have received IRB approval and submit the following documents:
  - o IRB approval letter
  - o IRB approved consent forms
  - o Signed Protocol Signature Page
  - o Laboratory normal ranges
  - o Estimated accrual
  - o Names of staff who will need access to EDC, RhoRAND, and/or RhoLAB
  - o Number of printed brochures needed (if applicable)
- ❑ Ensure that your site has a barcode reader from Rho; a barcode reader will be provided if one has not been provided for another CSCC study
- ❑ Submit Order Forms for:
  - o Initial supply of HU
  - o Initial supply of Mg
  - o Initial supply of lab kits and pharmacy supplies (bottle stoppers, dosing syringes, etc)
- ❑ Schedule Site Initiation Visit (SIV)
- ❑ Site Pharmacist Training

Ongoing

- ❑ Ensure timely entry of data into the EDC system
- ❑ Report SAEs per regulations
- ❑ Biweekly site calls from the SDMC
- ❑ Respond to data queries
- ❑ Participate in monthly Study Coordinator teleconferences
- ❑ Re-order study drug and lab kits as needed
- ❑ Monitoring Visits
- ❑ Submit updated documents to the SDMC as necessary:
  - o CVs & professional license for all PIs and Sub-I's listed on the 1572
  - o IRB approval for any protocol revisions; include corresponding Protocol Signature page
- ❑ Ensure the Site Signature & Responsibility Log is kept up to date
- ❑ Annual IRB renewals or amendments as needed

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Effectiveness of Hydroxyurea and Magnesium Pidolate Alone and in Combination in Hemoglobin SC Disease: A Phase II Trial (CHAMPS)

Table of Activities by Visit

Visit #	Week/Timing of Visit	Clinical Evaluations[1]	Clinical Outcomes[2]	Hematology Panel (CBC)[3]	Adverse Events	Pregnancy Test	Chemistry Panel[4]	Urin-alysis	Central Labs[5]
		All Visits	*All Visits*	*All Visits*	*All Visits*	*Visits 1-15*	*Visits 1, 2, 6, 8, 10, 12, 14, 16*	*Visits 2,10,16*	*Visits 1, 2, 6, 8, 10, 15*
1	Week -1	X	X	X	X	X	X		X
2	Baseline (Visit 1 + 1-3 wks)	X	X	X	X	X	X	X	X
3	Week 2 ± 4 days	X	X	X	X	X			
4	Week 4 ± 4 days	X	X	X	X	X			
5	Week 6 ± 4 days	X	X	X	X	X			
6	**Week 8 ± 4 days**	**X**	**X**	**X**	**X**	**X**	**X**		**X**
7	Month 3 ± 8 days	X	X	X	X	X			
8	Month 4 ± 8 days	X	X	X	X	X	X		X
9	Month 5 ± 8 days	X	X	X	X	X			
10	Month 6 ± 8 days	X	X	X	X	X	X	X	X
11	Month 7 ± 8 days	X	X	X	X	X			
12	Month 8 ± 8 days	X	X	X	X	X	X		
13	Month 9 ± 8 days	X	X	X	X	X			
14	Mth 10 ± 8 days	X	X	X	X	X	X		
15	Mth 11 ± 8 days	X	X	X	X	X			X
16	Mth 12 ± 8 days	X	X	X	X		X	X	

Notes

- Visit 1 also includes electrophoresis and an HIV test.
- If a subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.

1. Clinical Evaluations: brief physical exam to ensure general health
2. Clinical Outcomes: pain crises, ACS, hospital admissions, transfusions, deaths, clinical stroke, acute splenic sequestration. Cancer and neuroimaging collected at Visits 1, 2, 7, 10, 13, and 16.
3. Hematology Panel (CBC): Hemoglobin, Hematocrit, RBC, WBC, MCV, MCHC, Platelet Count, % Retic OR ARC, ANC
4. Chemistry Panel: Sodium, Potassium, Chloride, CO_2, BUN, Creatinine, Calcium, SGPT/ALT, Alk phosphatase, Total bilirubin, Total protein, Albumin, LDH
5. Central labs: for each visit with central labs, 3 vacutainers of blood will be sent to Boston (Brugnara) and 1 vacutainer of blood will be sent to Duke (Telen). Part of the specimen sent to the Boston (Brugnara) lab after Visit 1 will be forwarded to another central lab in Boston (Chui) for the α-Gene measurement. For the first 40 patients enrolled into the study, part of the specimen sent to Brugnara's lab will be sent to Italy (DeFranceschi) for additional laboratory analyses to examine red cell membrane kinase activity and oxygen damage to red cell membrane proteins.

CHAMPS Study Visit Checklist - All Study Visits

Comprehensive Sickle Cell Centers Clinical Trials Consortium

Visit One (Week –1)
- ❑ Electrophoresis*
- ❑ HIV Test
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Chemistry Panel
- ❑ Boston (Brugnara) Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke (Telen) Lab: 1 full 5-mL lavender vacutainer
- ❑ α gene measurement (part of the specimen sent to the Boston lab will be forwarded to another central lab for this value)

***If the subject is transfused, electrophoresis is repeated as needed until the subject's Hb %A ≤ 10%.**

Visit Two (Baseline: Visit 1 + 1-3 weeks)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Administer first dose of study drug
- ❑ Distribute Study Drug Log to Subject
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Three (Week 2 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check

Visit Four (Week 4 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit Five (Week 6 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ CBC
- ❑ Pregnancy Test
- ❑ Toxicity Check

Visit Six (Week 8 ± 4 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Seven (Month 3 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit Eight (Month 4 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit Nine (Month 5 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 10 (Month 6 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit 11 (Month 7 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 12 (Month 8 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug
- ❑ Chemistry Panel

Visit 13 (Month 9 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer study drug

Visit 14 (Month 10 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Administer last monthly supply of study drug
- ❑ Chemistry Panel

Visit 15 (Month 11 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Pregnancy Test
- ❑ Toxicity Check
- ❑ Collect unused study drug and Study Drug Log
- ❑ Boston Lab: 2 half-full 10-mL lavender vacutainers, 1 full 5-mL green vacutainer
- ❑ Duke Lab: 1 full 5-mL lavender vacutainer

Visit 16 (Month 12 ± 8 days)
- ❑ Clinical Evaluations
- ❑ Clinical Outcomes
- ❑ Hematology Panel
- ❑ Chemistry Panel
- ❑ Urinalysis (U/A)
- ❑ Toxicity Check

Note: Toxicity Visits, AEs for Painful Crisis, AEs, SAEs, Concomitant Medications, and Protocol Deviations are completed as needed.

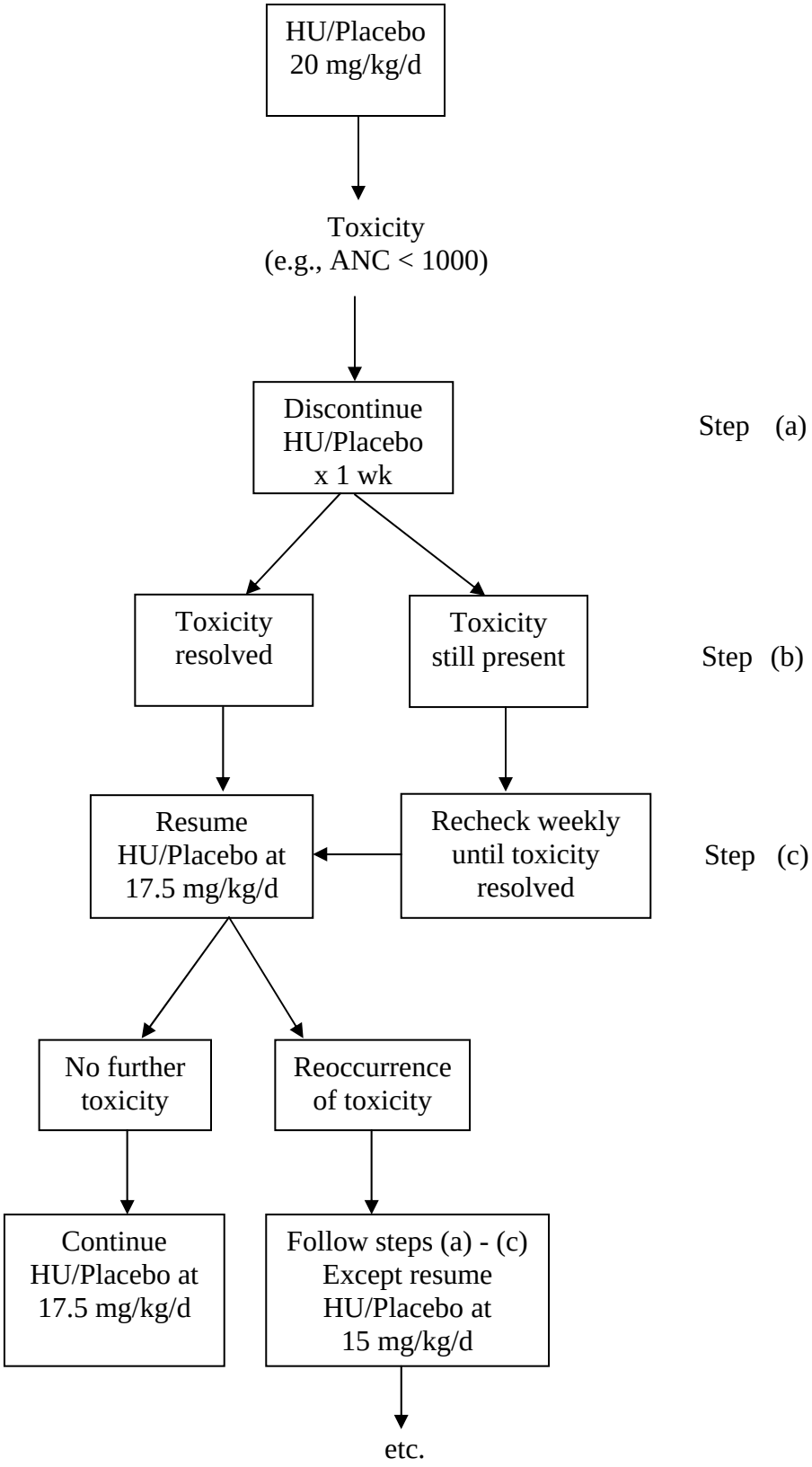
HYDROXYUREA (AND PLACEBO) DOSING AND DOSE ADJUSTMENT TABLE

Dose and # of caps refer to both HU and Placebo

caps = number of capsules per day. If more than one number, the subject should take the first number on the first day, the second on the 2nd day, etc, and then repeat. E.g. if dose is 2/1/1: 2 pills on Day One, 1 pill on Day Two, 1 pill on Day Three, then repeat (2 pills on Day Four, 1 pill on Day Five, 1 pill on Day Six, repeat).
Actual doses below are close approximations of the prescribed dose. Equivalent dosing may be used if necessary. E.g., a child with a dose of 500 mg who cannot swallow the large capsules may be given alternate a dose of 400 mg with a dose of 600 mg.

		20/mg/kg/d			17.5 mg/kg/d (1st Toxicity)			15 mg/kg/d (2nd Toxicity)			12.5 mg/kg/d (3rd Toxicity)		
Wt. (kg)	Wt. Range (kg)	HU/ Placebo Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)	Dose (mg)	500 mg (# caps)	200 mg (# caps)
15	12.6 - 17.5	300		2/1	262.5		2/1/1	225		2/1/1/1/1/1	187.5		1
20	17.6 - 22.5	400		2	350		2/2/2/1	300		2/1	250	1/0	
25	22.6 - 27.5	500	1		437.5		3/2/2/2	375		2	312.5		2/1
30	27.6 - 32.5	600		3	525	1		450		2	375		2
35	32.6 - 37.5	700	1	1	612.5		3	525	1		437.5		2
40	37.6 - 42.5	800		4	700	1	1	600		3	500	1	
45	42.6 - 47.5	900	1	2	787.5		4	675	1	1	562.5		3
50	47.6 - 52.5	1000	2		875		4	750	1	1	625		3
55	52.6 - 57.5	1100	1	3	962.5	1	2	825		4	687.5	1	1
60	57.6 - 62.5	1200	2	1	1050	2		900	1	2	750	1	1
65	62.6 - 67.5	1300	1	4	1137.5	1	3	975	2		812.5		4
70	67.6 - 72.5	1400	2	2	1225	2	1	1050	2		875	1	2
75	72.6 - 77.5	1500	3		1312.5	1	4	1125	1	3	937.5	1	2
80	77.6 - 82.5	1600	2	3	1400	2	2	1200	2	1	1000	2	
85	82.6 - 87.5	1700	3	1	1487.5	2	2	1275	1	4	1062	1	3
90	87.6 - 92.5	1800	2	4	1575	3		1350	2	2	1125	1	3
95	92.6 - 97.5	1900	3	2	1662.5	2	3	1425	2	2	1187.5	2	1
100	97.6 - 102.5	2000	4		1750	3	1	1500	3		1250	3/2	
105	102.6 - 107.5	2100	3	3	1837.5	2	4	1575	2	3	1312.5	1	4
110	107.6 - 112.5	2200	4	1	1925	3	2	1650	3	1	1375	2	2
115	112.6 - 117.5	2300	3	4	2012.5	4		1725	3	1	1437.5	2	2
120	117.6 - 122.5	2400	4	2	2100	3	3	1800	2	4	1500	3	
125	122.6 - 127.5	2500	5		2187.5	3	3	1875	3	2	1562.5	2	3

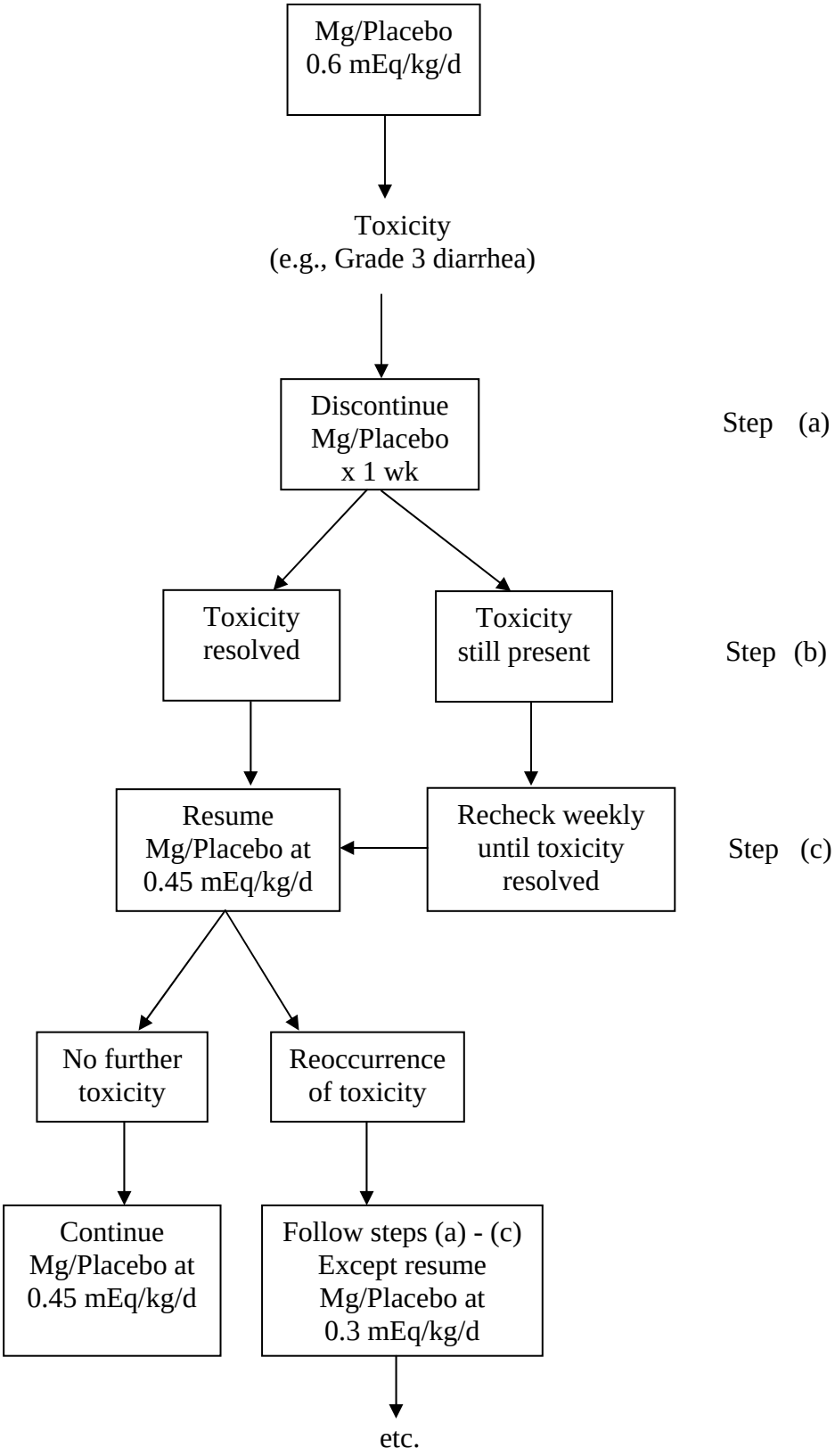
HU/Placebo Dose Modification for Toxicity



MAGNESIUM PIDOLATE (AND PLACEBO) DOSING & DOSE ADJUSTMENT TABLE

Wt. (kg)	Wt. Range (kg)	Initial Dose Mg Pidolate 0.3 mEq/kg BID		Dose after 1st Toxicity Mg Pidolate 0.225 mEq/kg BID		Dose after 2nd Toxicity Mg Pidolate 0.15 mEq/kg BID	
		(mEq)	(ml)	(mEq)	(ml)	(mEq)	(ml)
15	12.6 - 17.5	4.5	2.2	3.4	1.7	2.2	1.1
20	17.6 - 22.5	6.0	3.0	4.5	2.2	3.0	1.5
25	22.6 - 27.5	7.5	3.7	5.6	2.8	3.7	1.9
30	27.6 - 32.5	9.0	4.5	6.8	3.4	4.5	2.2
35	32.6 - 37.5	10.5	5.2	7.9	3.9	5.2	2.6
40	37.6 - 42.5	12.0	6.0	9.0	4.5	6.0	3.0
45	42.6 - 47.5	13.5	6.7	10.1	5.0	6.7	3.4
50	47.6 - 52.5	15.0	7.5	11.2	5.6	7.5	3.8
55	52.6 - 57.5	16.5	8.2	12.4	6.2	8.2	4.1
60	57.6 - 62.5	18.0	9.0	13.5	6.7	9.0	4.5
65	62.6 - 67.5	19.5	9.7	14.6	7.3	9.7	4.9
70	67.6 - 72.5	21.0	10.5	15.8	7.9	10.5	5.2
75	72.6 - 77.5	22.5	11.2	16.9	8.4	11.2	5.6
80	77.6 - 82.5	24.0	12.0	18.0	9.0	12.0	6.0
85	82.6 - 87.5	25.5	12.7	19.1	9.5	12.7	6.4
90	87.6 - 92.5	27.0	13.5	20.2	10.1	13.5	6.8
95	92.6 - 97.5	28.5	14.2	21.4	10.7	14.2	7.1
100	97.6 - 102.5	30.0	15.0	22.5	11.2	15.0	7.5
105	102.6 - 107.5	31.5	15.7	23.6	11.8	15.7	7.9
110	107.6 - 112.5	33.0	16.5	24.7	12.3	16.5	8.2
115	112.6 - 117.5	34.5	17.2	25.9	12.9	17.2	8.6
120	117.6 - 122.5	36.0	18.0	27.0	13.5	18.0	9.0
125	122.6 - 127.5	37.5	18.7	28.1	14.0	18.7	9.4

Mg/Placebo Dose Modification for Toxicity



CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Specimen Collection and Shipping to the Duke Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 5-mL lavender-top vacutainer; collect blood into the vacutainer *until it is full*. Do NOT remove the rubber top of the vacutainer.
2. Place one barcode label on the vacutainer and place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
3. Log into RhoLAB, select the correct subject ID, and enter the barcode number on the vacutainer into the system via the barcode scanner.
4. Create a shipment within RhoLAB for the single vacutainer going to Duke and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
5. Insert the vacutainer into the Aqui-Pak absorbent pouch.
6. Roll up the Aqui-Pak and insert it into the small 95 kPa canister.
7. Place the small 95 kPa canister into the "Biohazard" ziplock bag and place it upright inside the foam cooler.
8. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
9. Repeat Step 8.
10. Place the two bags of ice around the small, bagged 95 kPa canister.
11. Close the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
12. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Duke lab as the recipient of the 1 5-mL lavender-top vacutainer.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
13. Place the return label on top of the foam cooler.
14. Tape the outer cardboard box shut.
15. Apply the "UN3373 Biological Substance" label to outside of box.
16. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
17. Apply "biohazard" label to outside of box.
18. Apply "LAB OPEN IMMEDIATELY CHAMPS STUDY" label to the outside of the box.
19. Attach completed air bill to the top of the outside of the box and send to shipping area.

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Durham, NC 27710
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Comprehensive Sickle Cell Centers
Clinical Trials Consortium

Specimen Collection and Shipping to the Boston Central Lab

June 13, 2007

1. Insert the needle into the rubber top of the 6-mL green-top vacutainer and collect blood into the vacutainer *until it is almost full*. Do NOT remove the rubber top of the vacutainer.
2. Insert the needle into the rubber top of EACH of the 10-mL purple-top vacutainers and collect blood approximately half way into the vacutainer. Do NOT remove the rubber top of the vacutainer.
3. Place one barcode label on each of the three vacutainers, place the duplicate barcode label on the "RhoLAB data collection sheet" (kept in the Subject Study Binder).
4. Log into RhoLAB, select the correct subject ID, and add the barcode numbers on each of the 3 vacutainers into the system via the barcode scanner (this will be done simultaneously with the 5-mL lavender vacutainer going to the Duke lab).
5. Create a shipment within RhoLAB for all three vacutainers going to Boston (Brugnara) and print a copy of the packing slip with the shipment ID # and shipment contents listed on it.
6. Insert each of the three vacutainers into one Aqui-Pak absorbent pouch.
7. Roll up the Aqui-Pak tube-over-tube and insert it into the small 95 kPa canister.
8. Place the small 95 kPa canister into Biohazard plastic bag and place it upright inside the foam cooler.
9. Fill one 12 x 12 ziplock bag with ice. Place this bag of ice into an empty ziplock bag (so that the ice is double-bagged).
10. Repeat Step 9.
11. Place the two bags of ice around the small 95 kPa canister.
12. Seal the foam cooler and tape the packing slip generated by RhoLAB to the top of the foam cooler.
13. Log into Fedex.com using the username and password created by the SDMC for study coordinator or personnel responsible for shipping specimens to the central labs.
    - Select the Boston (Brugnara) lab as the recipient of the 3 vacutainers.
    - Check the box beside "Process return Label" under "More shipment details" section at the bottom.
14. Place the return label on top of the foam cooler.
15. Tape the outer cardboard box shut.
16. Apply the "UN3373 Biological Substance" label to outside of box.
17. Apply the "up arrow" labels to the opposite sides of box (narrow box ends).
18. Apply the "biohazard" label to outside of box.
19. Apply the "LAB OPEN IMMEDIATELY HU-MG STUDY" label to the outside of the box.
20. Attach completed air bill to the outside of the box and send to the shipping area.

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CSCC
Hydroxyurea & Magnesium Pidolate Protocol (CHAMPS)

CRF and Completion Guidelines

Information about the forms

General information

- This study is using a remote data entry system. All data collected for this study will be entered into the CSCC's Electronic Data Capture System website. Data entry should be completed within one week of data collection.

Header information

- Some forms require the date of visit or assessment.
- The patient's CSCC ID number must be recorded on each individual CRF and will be pre-populated by the EDC system.

Dates

- Dates should be recorded in the following format: **dd/mmm/yy** (i.e., 22/JUN/06).
  Record leading zeros where applicable.
- If a complete date is unknown, record the date part(s) that are known and leave the rest blank. In some cases, a message will prompt the user to review the blank date or date parts. The user should override this validation check by clicking the override button. A comment explaining why the required lab value cannot be provided should be entered at this point.

Specific fields or blocks of information on a form that were not collected

- Leave the fields blank. In some cases, an override comment as described above will be required.

Numeric fields

- Rounding rules: If the digits to the right of the decimal in any number are greater than the number of boxes available for data entry of the number, then the value should be rounded to the correct number of places, using conventional rounding rules. Example: A lab value for hemoglobin of 12.06 g/dL will be entered as 12.1 g/dL and a lab value of 12.03 g/dL will be entered as 12.0 g/dL.

Source documentation

- Store all original study-related materials (case report forms, lab reports, etc.) in the subject's research record. File a copy in the subject's medical record and send copies to Rho or the DSMB as needed. If a case report form page was completed on paper before entering the data into the EDC system then store that CRF page in the subject's research record.
- Delete or completely mark out subject identifiers on all study materials. Be sure that the subject ID number is present.

CRF Completion Guidelines

Information about the EDC system

General information

- All information is to be entered via the CSCC's Electronic Data Capture (EDC) website.
- The subject ID and site header information will be automatically displayed when entering data in the EDC system.

To access the EDC system

Access will be granted to the EDC system once a site has all necessary documents to begin enrollment. To access the EDC system once a site has approval:

- Log on to the secure CSCC website.
- Choose "**CHAMPS"** from the list of studies on the right side of the screen.
- Under the heading "EDC Links", choose "Data Entry -> "**CHAMPS"**
- Open the subject for which you want to enter data by selecting subject ID number (for a subject already enrolled in this study), importing a subject from another CSCC study, or enrolling a new patient in the **CHAMPS** study.
- Select the page for which data is to be entered.
- Remember to log out when you are finished.

Corrections to data

- Open the page in the EDC system where the data was originally entered. Find the field and change the entry. Click the "Update" button at the bottom of the screen in order to submit corrections to the database.

Help documents

- Click the "EDC HELP" link in the gray navigation menu on the left side of the EDC screen for help navigating the EDC system.
- Each CRF page has a "Form completion help" link at the bottom of the page which contains information about completing that CRF page.

CSCC
Comprehensive Sickle Cell Centers
Clinical Trials Consortium

CHAMPS STUDY

Rho, inc.

Product Request Form

NOTE TO SITES: *Fax completed form to Therapak at 626-357-5911 or email to khawk@therapak.com.*

Shipper:
Therapak Corporation 1801 Highland Ave., Unit L Duarte, CA 91010 Phone: (626) 357-5900 Fax: (626) 357-5911 Email: khawk@therapak.com

Rho Project Manager: *(Sites, please do not fax orders here)*	
Name:	Jason Davis / Cathie Snyder
E-mail: cc:	jmdavis@rhoworld.com cathie_snyder@rhoworld.com
Phone:	(919) 408-8000 x 344 / x 291
Fax:	(919) 287-0126

Sponsor:	NHLBI
Protocol Name:	CHAMPS

Date Order Placed:
Date Needed at Site:

Ship To: Site ID:
Phone:

Shipping Method:	
FedEx	
Freight:	Bill to RHO acct. # 1927-2649-2
Reference:	Rho/CHAMPS/6703

ITEM #	ITEM DESCRIPTION	Max Order[1]	QTY.	LOT NO.	EXPIRATION
23027	Small 95 kPa Canister w/ Cap	3			
33622	Blood Sample Collection Kit[2]	6			
33623	Refrigerated (Wet Ice) Shipping Kit[3]	3			
33638	Accessory Kit[4] (Order this kit **OR** items with "CS" in the item #. Do not order both.)	2			
55521-CS	Mark-a-Dose Labels (order in increments of 100)	200			
79289-CS	5-mL Dosing Syringe (order in increments of 50)	100			
79290-CS	10-mL Dosing Syringe (order in increments of 25)	50			
79291-CS	20-mL Dosing Syringe (order in increments of 25)	50			
23013-CS	Press-In Bottle Adapters (for Mg bottles)	50			
57016-CS	7-Day Pill Dispensers	10			
50266	*Domestic Site Distribution Fee*				

1. Orders should not exceed the maximum order quantity. Contact Jason Davis at the SDMC if you need more than the maximum.

2. Blood Sample Collection Kit
   - One 6-mL green vacutainer
   - One 5-mL lavender vacutainer
   - Two 10-mL lavender vacutainer
   - Two 4-bay Aquipak (absorbent tube shuttle)
   - Eight 12 x 12 ziplock bags (to contain ice)
   - Two 6 x 9 ziplock bags (to contain plastic canister)
   - Two FedEx airbill pouches

3. Refrigerated (Wet Ice) Shipping Kit
   - One small foam cooler
   - One cardboard box for small cooler
   - One small canister (to place the 4-bay Aquipak enclosed in the 6 x 9 ziplock bag)
   - One Biohazard label
   - One UN3373 Diagnostic Specimens Label
   - Two Up Arrow Labels
   - One "LAB OPEN IMMEDIATELY CHAMPS STUDY"

4. Accessory Kit - Supply of all pharmacy accessories. Pharmacy accessories are identified above with "CS" in the item #.
   - 200 Mark-a-Dose Labels
   - 50 5-mL Dosing Syringes
   - 100 10-mL Dosing Syringes
   - 50 20-mL Dosing Syringes
   - 40 Press-In Bottle Adapters
   - 20 7-Day Pill Dispensers

CHAMPS STUDY

Product Request Form

NOTE TO SITES: *Fax completed form to Therapak at 626-357-5911 or email to rschulze@therapak.com*

Shipper:
Therapak Corporation 1801 Highland Ave., Unit L Duarte, CA 91010 Phone: (626) 357-5900 Fax: (626) 357-5911 Email: rschulze@therapak.com

Rho Project Manager: *(Sites, please do not fax orders here)*	
Name:	Emily Kunka / Cathie Snyder
E-mail: cc:	Emily_Kunka@rhoworld.com Cathie_Snyder@rhoworld.com
Phone:	(919) 408-8000 x 585 / x 291
Fax:	(919) 287-0126

Sponsor: NHLBI
Protocol Name: CHAMPS

Date Order Placed:
Date Needed at Site:

Ship To: Site ID:
Phone:

Shipping Method:
FedEx
Freight:
Reference: Rho/CHAMPS/6203

ITEM #	ITEM DESCRIPTION	Max Order*	QTY.	LOT NO.	EXPIRATION
23027	Small 95 kPa Canister w/ Cap	3			
33622	Blood Sample Collection Kit[1]	10			
33623	Refrigerated (Wet Ice) Shipping Kit[2]	3			
33638	Accessory Kit[3] (Order this kit **OR** items with "CS" in the item #. Do not order both.)	2			
55521-CS	Mark-a-Dose Labels (order in increments of 100)	200			
79289-CS	5-mL Dosing Syringe (order in increments of 50)	100			
79290-CS	10-mL Dosing Syringe (order in increments of 25)	50			
79291-CS	20-mL Dosing Syringe (order in increments of 25)	50			
23013-CS	Press-In Bottle Adapters (for Mg bottles)	50			
57016-CS	7-Day Pill Dispensers	10			
50266	*Domestic Site Distribution Fee*				

* Contact Emily Kunka at the SDMC if you need to order more than the maximum quantity listed above.

1. Blood Sample Collection Kit
   - One 6-mL green vacutainer
   - One 5-mL lavender vacutainer
   - Two 10-mL lavender vacutainer
   - Two 4-bay Aquipak (absorbent tube shuttle)
   - Eight 12 x 12 ziplock bags (to contain ice)
   - Two 6 x 9 ziplock bags (to contain plastic canister)
   - Two FedEx airbill pouches

2. Refrigerated (Wet Ice) Shipping Kit
   - One small foam cooler
   - One cardboard box for small cooler
   - One small canister (to place the 4-bay Aquipak enclosed in the 6 x 9 ziplock bag)
   - One Biohazard label
   - One UN3373 Diagnostic Specimens Label
   - Two Up Arrow Labels
   - One "LAB OPEN IMMEDIATELY CHAMPS STUDY"

3. Accessory Kit - Supply of all pharmacy accessories. Pharmacy accessories are identified above with "CS" in the item #.
   - 200 Mark-a-Dose Labels
   - 50 5-mL Dosing Syringes
   - 100 10-mL Dosing Syringes
   - 50 20-mL Dosing Syringes
   - 40 Press-In Bottle Adapters
   - 20 7-Day Pill Dispensers