Abbreviated Title: Medication Adherence in NF1

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Title: Pilot Study of Medication Adherence in Children, Adolescents, and Adults with Neurofibromatosis Type 1 (NF1) on Clinical Treatment Trials

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PRÉCIS

Background:

- Neurofibromatosis type 1 (NF1) is a genetic disorder that affects approximately 1 in 3,500 individuals and is associated with a broad variety of symptoms and physical findings.
- Plexiform neurofibromas (PN) are histologically benign tumors which occur in 25-50% of patients with NF1 and can lead to significant morbidity.
- Oral therapeutic options for the treatment of plexiform neurofibromas are being actively developed, however early clinical data indicate that prolonged treatment over the course of months to years will likely be needed to maintain clinical efficacy
- Long-term medication adherence is an ongoing challenge for patients with many types of chronic illness, and clinical experience makes us strongly suspect patients with NF1 will likely have this issue as well.
- In other diseases, such as HIV and Acute Lymphoblastic Leukemia, decreased medication adherence has been associated with poorer clinical outcomes, and this may be the case for NF1 as well.
- The medication event monitoring systems (MEMS^{TM}) uses a computerized method of tracking the dates and times of a pill bottle being opened, and has been shown to be a more accurate measure of medication adherence than patient diaries or pill counts in other patient populations.
- Assessing medication adherence over time in this unique population will be essential for assessing any impact on medical outcomes, identifying potential behavioral interventions, and targeting patients most at risk for nonadherence moving forward.

Objective:

- To establish the feasibility of using MEMS^{TM} to monitor medication adherence in the NF1 population

Eligibility:

- Subjects must have a diagnosis of NF1 and be between 3 and 59 years of age
- Participants must be enrolled on a clinical trial for an oral medication in pill (tablet or capsule) form directed at the treatment of plexiform neurofibroma(s)

Design:

- This single-site, longitudinal study will recruit children and adults with NF1 who are currently enrolled in a treatment protocol for a drug targeting PN volume reduction.
- MEMS^{TM} caps will be used to monitor adherence over time along with patient diaries and pill counts.
- Patients with MEMS^{TM} cap data indicating <90% adherence at any study visit (typically across 3 – 6 cycles) will be administered a measure assessing barriers to adherence

electronically and will be interviewed to evaluate what factors might contribute to decreased medication adherence and what potential interventions they consider useful.

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1.1.1 Primary Objective

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1.1.2.2 To identify patient characteristics and/or time periods during treatment that predispose to poor medication adherence

1.1.3 Exploratory Objectives

1.1.3.1 To compare adherence rates between MEMS™ caps, pill counts, and patient diaries

1.1.3.2 To compare response to therapy between patients that are adherent to medication (≥90% adherence by MEMS™) with patients that are non-adherent to medication (<90% adherence by MEMS™)

1.1.3.3 To compare adherence rates across different age groups (e.g., patients < 12 vs. ≥ 12 years old)

1.2 BACKGROUND AND RATIONALE

1.2.1 Emerging Therapies in Neurofibromatosis Type 1

Neurofibromatosis 1 (NF1) is an autosomal dominant disorder with an incidence of 1:3500 in the United States[1]. One of the cardinal features of NF1 is the development of histologically benign peripheral nerve sheath tumors called plexiform neurofibromas (PN) in 25-50% of individuals with NF1[1,2]. PN are a major source of morbidity for many patients. The only current standard treatment for these tumors is surgical resection, yet many of the tumors are inoperable as they are often infiltrative and intertwined with vital vascular and nervous system structures. Recent studies of selumetinib (AZD6244), an oral specific MEK1/2 inhibitor, have shown promise in the treatment of PN. As this drug and other potential therapeutic options become available for this unique patient population, assessing and ensuring adherence with prescribed medication regimens will be essential, with implications for clinical trials and for prescribed usage. The current study aims to (1) document longitudinal patterns of adherence to oral therapy for PNs among children, adolescents, and young adults with NF1, and to (2) identify patient characteristics and/or time periods during therapy that are associated with an increased risk of medication non-adherence.

The occurrence of PN tumors in NF1 cause substantial morbidity, including, but not limited to, disfigurement, impairment of nerve function, and pain[3,4]. MEK inhibitors, such as selumetinib, inhibit the activity of isolated MEK to phosphorylate extracellular signal-regulated kinase (ERK) 2 in enzyme assays. In the Phase I portion of the NIH study of selumetinib for pediatric patients with inoperable plexiform neurofibromas, 17 of 24 patients (71%) had confirmed partial

responses defined as a PN volume decrease ≥ 20% compared to baseline [5]. Notably, while many patients began to have clinical benefit within the first year of therapy, the maximum PN volume decrease was observed after an average of 18.9 cycles (median 19; range 5 - 46). This finding makes biological sense, as PN usually grow slowly over the course of years, and therefore will likely require treatment for prolonged time periods to see shrinkage. The recommended pediatric dosing regimen for selumetinib is 25 mg/m^2 by mouth twice daily on continuous 28-day cycles. While generally well tolerated, we know that patients on the phase I selumetinib trial who required dose reductions and/or drug holds for toxicity tended to have tumor regrowth, which indicates the need for long term medication adherence to maintain benefit. While the most rapid progression of PN occurs in young children, adolescents and adults can have continued PN growth and significant PN related morbidity that may impact their quality of life, which may be improved by decreasing their PN burden [6,7]. Figure 1 shows significant tumor regrowth in patients after dose reductions in two phase I patients.

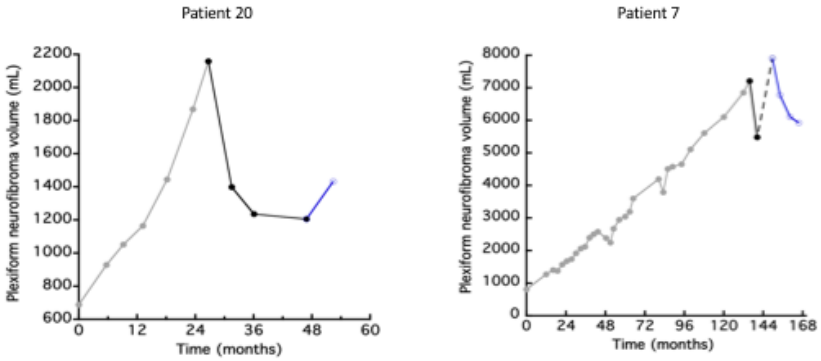


Figure 1 Examples of PN Regrowth after Selumetinib Dose Reduction or Drug Hold. Volumetric MRI analysis of plexiform neurofibroma growth prior to treatment (grey symbols), shrinkage on treatment with selumetinib (black symbols). Patient 20: plexiform neurofibroma volume increase after dose reduction (blue open symbol). Patient 7: plexiform neurofibroma volume increase after holding selumetinib for dose-limiting toxicity (dashed line), and volume decrease after restarting selumetinib at reduced dose.

1.2.2 Importance of Medication Adherence

Adherence to oral therapy is essential during clinical trials to ensure that researchers are measuring the effects of the drug when taken as prescribed. High adherence will also be essential when these medications become available following FDA approval, since poor adherence may result in tumor regrowth. Previous studies looking at medication adherence in pediatric patients with other chronic illnesses have shown that average adherence may be as low as 50%[8]. Moreover, evidence suggests that the complexity of the regimen (i.e., intermittent dosing, food restrictions) can impact adherence [9,10], and this may be particularly important to consider in individuals with NF1 who have learning disabilities. Specific studies that have evaluated adherence to medications needed for long periods of time, such as anti-retroviral therapies for HIV and maintenance chemotherapy for acute lymphoblastic leukemia (ALL), have elucidated some of the difficulties in both assessing and maintaining drug adherence in various pediatric populations[11,12], and adherence often declines over time for substantial percentages of patients[13,14]. Fluctuations in adherence rates may be particularly apparent during the transition

from adolescence into young adulthood[14]. The assessment of treatment adherence is now recognized as a standard of care in pediatric oncology[15].

Of note, in the studies of patients with ALL, those with < 95% medication adherence during maintenance chemotherapy were found to have a 2.7 fold increased risk of relapse[12]. We strongly suspect that adherence will be equally important in the NF1 patient population, as illustrated by the tumor regrowth we have seen in patients that have required drug holds and/or dose reductions on the phase I study of selumetinib (**Figure 1**). Identifying patterns of medication adherence in the NF1 population will enable researchers to develop interventions targeting the patients and/or time periods that are most at risk for non-adherence.

1.2.2.1 Medication Adherence Monitoring

Most clinical trials that currently attempt to monitor adherence utilize self-reported patient diaries and researcher-performed pill counts to do so; however, extensive prior research [11] and our experience with these methods has shown them to be inconsistent and to overestimate adherence. One method for more objective monitoring of adherence is the use of a medication event monitoring system (MEMS™). Through a microchip implanted in the pill bottle cap, this system uses a computerized method of tracking the dates and times of the pill bottle being opened. A recent Children's Oncology Group Study that compared reporting of maintenance 6-MP medication adherence by self-reported diaries with MEMS™ data showed that 23.6% of 416 patients over-reported their adherence (self-report was higher than MEMS by ≥ 5 days/month for ≥ 50% of study months).[16]

Use of MEMS™ among patients on NF1 clinical trials would allow us to more accurately track adherence to document patterns of change over time, and would allow us to more fully assess if there is any correlation between tumor response and medication adherence.

1.2.2.2 Preliminary Data

The phase I trial of selumetinib for patients with inoperable PN offered some unique preliminary insights into the medication adherence issues for this population. On the trial, patients were treated with selumetinib twice daily by mouth on continuous 28-day cycles. Medication adherence was recorded using pill counts and patient diaries. The number of doses missed by each patient per cycle was documented, and missed doses were characterized as related to nonadherence if the patient was not directed to hold drug by the study team. Of the 24 patients on the trial, 23 patients received at least 18 cycles of study drug. Of these 23 patients, 16 patients missed at least one dose of study drug due to nonadherence. For each patient, the total number of doses missed over the first three cycles was compared using a paired t-test to the total number of doses missed from cycles 15-18 for that patient, and there was a statistically significant increase in doses missed (average 1.3 doses per cycle missed in cycles 1-3 vs 2.7 doses per cycle missed in cycles 15-18, $p<0.05$). In addition, when all 17 patients who had missed doses were included, the percentage of missed doses per cycle increased over time, with only 0.5% of doses missed due to patient nonadherence by all patients in cycle 1 compared with 1.3% in cycle 18. When the percent of missed dosages is plotted over the first 24 cycles, a positive correlation is seen between number of missed medication doses and number of cycles on therapy ($R^2 = 0.2$) (**Figure 2**).

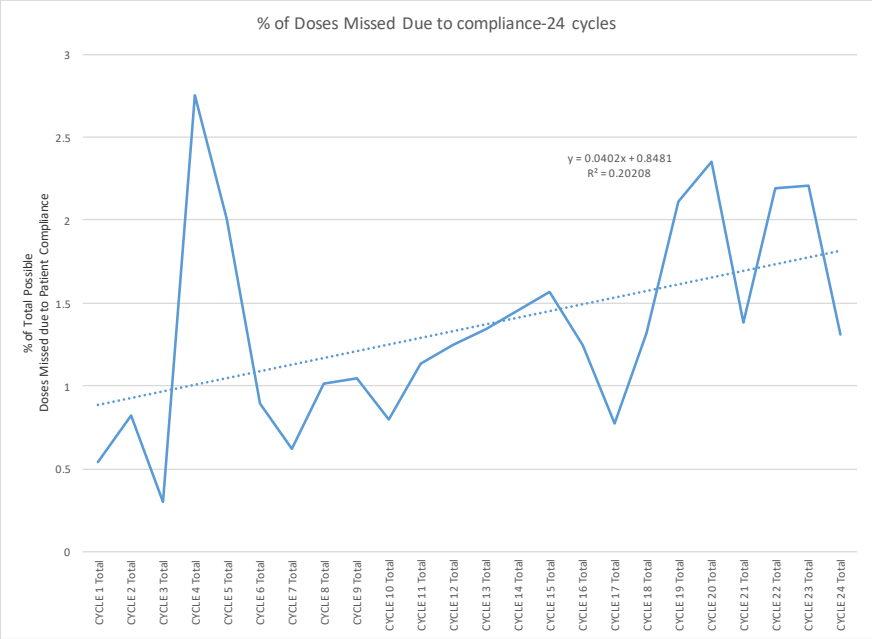


Figure 2: Correlation of missed medication doses with time on study drug. Percentage of missed doses due to patient adherence were calculated based on the total number of doses missed by all patients in a given cycle divided by the total number of possible doses patients were prescribed during that cycle. There is a general trend towards increasing percentage of missed doses over time, as seen over the course of 24 cycles in the figure above.

1.2.3 General Overview

This study will recruit children and adults with NF1 who are enrolled in a current or future treatment protocol for a drug targeting PN reduction. Patients will be invited to participate during a routine treatment protocol-mandated visit, ideally within one cycle of starting study drug. During this visit, patients (and caregivers of child patients) will complete a series of questionnaires as described in section **3.2**. The patients will also be instructed to begin using the medication event monitoring system (MEMS™) for the clinical trial drug only at initiation of study drug (or at beginning of next cycle) that will provide the researchers with a more objective measure of adherence for the study drug.

MEMS™ data will be collected at all routinely scheduled protocol re-staging visits (e.g., baseline, pre-cycle 5, pre-cycle 9, pre-cycle 13, and pre-cycle 19) which will include measurements of tumor volume. During these appointments, patients will return their MEMS caps and data from the caps will be uploaded onto a computer software system. These data will capture percentage of doses taken (doses taken/doses prescribed X 100).

Following each study visit, rates of adherence from the diaries, pill counts, and MEMS™ caps will be compared. If one or more methods suggest an adherence rate of less than 80%, the PI of the medical trial will be notified.

If the MEMS™ caps indicate medication adherence of <90% for one or more cycles of therapy, or another method (e.g., diaries) indicates <80% adherence, the patients will be electronically sent a Barriers to Adherence Questionnaire (**Appendix F**) to help pinpoint potential medication adherence related issues. This will be sent to the subject ideally within one week but no later than one month of the study data being received by the NIH team.

All patients will be invited to participate in individual interviews focused on medication adherence issues, either between cycles 8-12 or at the time of coming off study (whichever is later). For all patients, the interviews will focus on the issues leading to any missed doses (if applicable) as well as to gauge what the best approach might be to address these issues in a future interventional trial. We also will ask patients if they encountered any barriers to medication adherence during the course of the trial and if so, what techniques they used to overcome them.

At the end of the study, any patients who had not previously completed the Barriers to Adherence Questionnaire will be asked to do so.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria for Patient

2.1.1.1 Patients must be between 3 and 59 years of age at the time of the baseline assessment.

2.1.1.2 Patients must be enrolled on an NF1 clinical trial for an oral medication directed at the treatment of plexiform neurofibroma(s) (enrollment on this study to occur ideally within 1st cycle)

2.1.1.3 Patients must have regular access to a computer or electronic device (e.g., smartphone, tablet) with internet access.

2.1.1.4 Must have a parent or adult primary caregiver willing to participate in the study.

2.1.1.5 Ability of subject or parent/guardian to understand and the willingness to sign a written informed consent document.

2.1.1.6 Subjects must be able to read and comprehend the English language.

2.1.2 Exclusion Criteria for Patient

2.1.2.1 In the opinion of the PI or an AI, the subject has significant cognitive or emotional difficulties that would prevent them from being able to understand and/or participate fully in the study or complete the measures. Though these patients might be receiving assistance in taking medication from a caregiver, it is likely that their medication taking

routine would be significantly different from the general population of patients with NF1.

2.1.2.2 Patients receiving the study drug in liquid form, since the use of MEMS™ caps prohibits liquid dosing.

2.1.3 Inclusion Criteria for Parents or Caregivers

2.1.3.1 Must be a parent or primary caregiver of a child (or if applicable adult patient) of diagnosed with NF1 and enrolled on a clinical trial for oral medication.

2.1.3.2 Must have a child (or if applicable adult patient) willing to participate in the study

2.1.3.3 Must have regular access to a computer or electronic device (e.g., smartphone, tablet) with internet access.

2.1.3.4 Must be able to speak and understand English.

2.1.3.5 Ability of subject to understand and the willing to sign a written informed consent document.

2.1.4 Exclusion Criteria for Parent or Caregiver

None

2.1.5 Recruitment Strategies

This study will recruit children and adults with NF1 who are currently enrolled in a treatment protocol for an oral drug targeting PN reduction. Patients will be recruited during a routine treatment protocol-mandated visit, preferably immediately after consenting for the treatment protocol. This protocol may also be abstracted into a plain language announcement posted on NIH websites.

2.2 SCREENING EVALUATION

2.2.1 Screening activities performed prior to obtaining informed consent

Minimal risk activities that may be performed before the subject has signed a consent include the following:

- Email, written, in person or telephone communications with prospective subjects

A waiver of consent for these activities has been requested in section **7.5.1**.

2.2.2 Screening activities performed after a consent for screening has been signed

There are no further screening activities associated with this study.

2.3 PARTICIPANT REGISTRATION AND STATUS UPDATE PROCEDURES

Registration and status updates (e.g., when a participant is taken off protocol therapy and when a participant is taken off-study) will take place per CCR SOP ADCR-2, CCR Participant Registration & Status Updates found here.

2.4 ASSIGNMENT PROCEDURES

2.4.1 Cohorts

Number	Name	Description
1	Patients	Patients enrolled on an NF1 clinical trial for an oral medication directed at the treatment of plexiform neurofibroma(s)
2	Parents/Caregivers	Parent or caregiver of enrolling patient

2.4.2 Arms

Number	Name	Description
1	Intervention	Questionnaires and use of the medication event monitoring system (MEMS™)

2.4.3 Arm Assignment

Patients in cohort 1 and parents/caregivers in cohort 2 will be direction assigned to Arm 1, Intervention.

2.5 BASELINE EVALUATION

The following questionnaires will be required of all participants (See Section **3.2** for a complete description of these questionnaires):

Table 1: Questionnaires

Domain	Questionnaire Name	Respondent	Location	Completion Time*
Demographics	Background Information Form	Parents, Adult patients	**Appendix A** **Appendix B**	5 min
Recent Life Events	Life Events Checklist (LEC)	Parents, Adult patients	**Appendix C** **Appendix D**	3 min
NF1 Quality of Life	PROMIS (Depression, Pain Interference & Cognitive Functioning)	Parents, Adult patients, pediatric patients 8+	**Appendix E**	10 min
Pill Count Form	Pill Count form	Study team member	**Appendix H**	5 min
Medication Diary	Generic Medication Diary Form*	Parents, Adult patients	**Appendix G**	3 min

*If a medication diary form is included as part of the treatment protocol on which the patient is concurrently enrolled, this can be used in place of the generic form(s).

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

During the initial visit, patients, parents/caregivers of minors, and if applicable parents/caregivers of adult patients will complete a series of questionnaires as described in section **3.2**. The participants will also be instructed to begin using the medication event monitoring system (MEMS™) that will provide an objective measure of adherence for the study drug. Through a microchip implanted in the pill bottle cap, this system uses a computerized method of tracking the dates and times of the pill bottle being opened. The MEMS™ procedures have been widely used in numerous clinical trials assessing medication adherence [17,18]. If patients are provided two different pill bottles of study medication (e.g. two different capsule sizes) for a given cycle of therapy, one of the two bottles will be chosen by the study team to monitor with the MEMS™ cap and opening of that cap will be assumed to reflect the patient taking their complete prescribed dose. This will be noted as a (necessary) limitation to the MEMS™ procedures.

Patients/caregivers will be given a form to complete any time they take a dose of medication that does not correspond to a pill bottle opening (**Appendix I)** Patients will also be asked to complete a self-report daily diary of medication adherence throughout treatment or through 18 cycles of therapy (whichever is shorter) and pill counts will be performed at all standard treatment protocol visits during this time. If diaries are included on the primary treatment protocol, these will be utilized. If not, a generic diary (**Appendix G)** form will be provided. The pill count form (**Appendix H)** should be completed by the study team for each cycle for all participants, as this also contains information regarding any dose adjustments or changes. These forms should be collected/completed by the study team during each routine treatment protocol mandated follow up appointment. In addition, at these visits patients will return their MEMS™ caps and data from the caps will be uploaded onto a computer software system before being returned to the patient during that same visit. Although not anticipated, if there are scheduling difficulties prohibiting the return of the cap before the patient leaves the center, we will send the cap to the patient/family via Federal Express. It is recommended, but not required, that a patient bring their MEMS cap to any of these visits, if a patient forgets we will collect the data at the next visit during which they bring the cap to clinic.

Results of evaluations for disease response as per the primary treatment protocol will be recorded (e.g. tumor volume) at all restaging evaluations through 18 cycles of therapy. The response criteria defined by each specific treatment protocol will be used to determine if the patient had stable disease, partial response, complete response or disease progression while on study therapy.

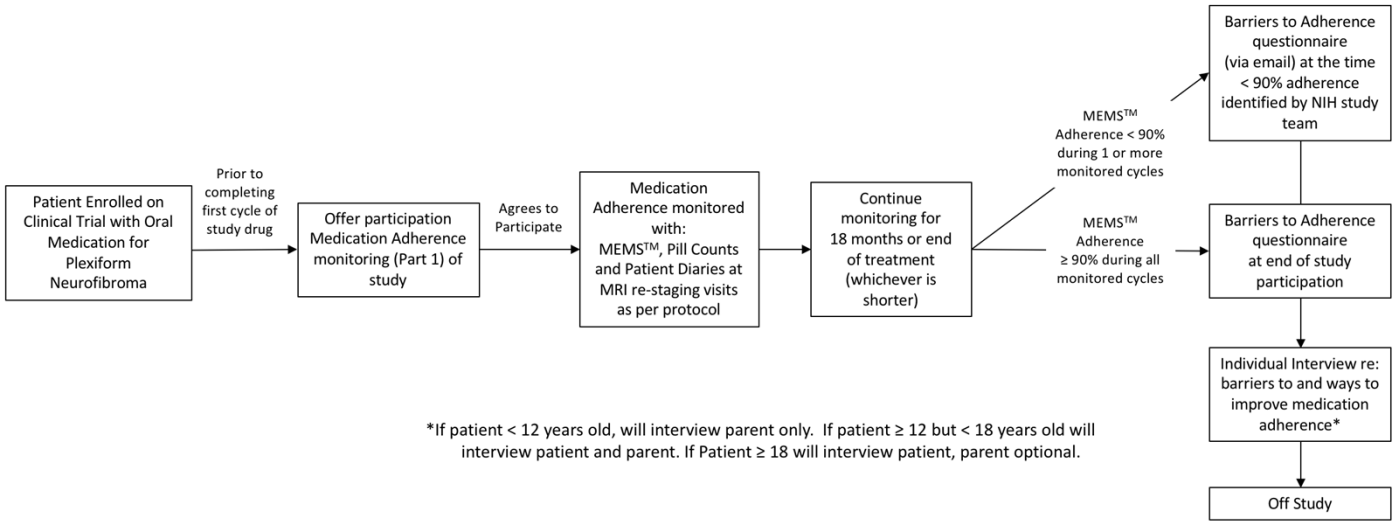
Following each study visit, rates of adherence from the diaries, pill counts, and MEMS caps will be compared. If one or more methods suggest an adherence rate of less than 80%, the PI of the medical trial will be notified via secure email or phone.

Patients with MEMS cap data indicating <90% adherence will be sent a Barriers to Adherence Questionnaire (**Appendix F**) electronically as close in time as possible (ideally within one week

and if feasible within one month) of the data being reported to the NIH study team. At the end of the study, any patients who had not previously completed the Barriers to Adherence Questionnaire will be asked to do so.

In addition, all patients will be invited to participate in an individual interview with a study team member to evaluate what factors might contribute to decreased medication adherence and what potential interventions they might consider useful. This interview will ideally be held between cycles 8-12 or at the time of coming off study (whichever is later). For study subjects < 12 years old, only the parent/caregiver of subjects will be interviewed. For patients ≥ 12 and < 18 years old, both parents and subjects will be interviewed. For patients > 18 years old, the subject will be interviewed, with parent/caregiver interview optional (e.g., depending on whether the patient lives with the parent). Twelve years was chosen as the minimum age for these interviews because it was thought that children younger than 12 may have difficulty with the telephone interview format and recall of the information. (**Figure 3**)

Figure 3: Study Schema



3.2 QUESTIONNAIRES

3.2.1 Background Information Form

The Background Information Form (**Appendix A** and **Appendix B**) is a questionnaire created by the study team that collects demographic and medical history variables including education, cognitive and psychiatric diagnoses, presence of pain and other NF-related symptoms, and level of independence. Adult patients ages 18+ years will complete the self-report version of this form and parents of pediatric patients (ages 3-17 years) will complete the Parent version on behalf of their child. This form is expected to take 5 minutes to complete.

3.2.2 Life Events Checklist

Since the occurrence of stressful life events can influence medication adherence[19], we are administering the Life Events Checklist (**Appendix C** and **Appendix D**), a list of significant life events where respondents indicate the events they have experienced within the past six months

[20]. The parent version of this form contains 27 items and the adult self-report version has 22 items. Given the time points of study visits on the NF consortium trials, we adapted this form to ask about events in the past three months. There is also a question at the end asking about level of overall stress (0-10). Adult patients ages 18+ years will complete the self-report version of this form and parents of pediatric patients (ages 3-17 years) will complete the Parent version on behalf of their child. This form takes about 3 minutes to complete.

3.2.3 Quality of Life

PROMIS forms will be administered to assess various aspects of quality of life (**Appendix E**) Versions of the PROMIS measures include adult self-reports for 18+ years, pediatric self-reports (ages 8 to 17 years), and parent reports for youth less than 18 years of age. Items ask the respondent to indicate the extent to which they have had particular problems over the past week, using a 1 – 5 Likert scale. The subscales that will be administered on this study include Depression (8 items on self-reports, 6 items on parent report), Pain Interference (6 items on adult self-report, 8 items on pediatric self-report and parent report), and Cognitive Function (8 items on adult self-report, 7 items on pediatric self-report and parent report). Mean scores for each subscale are converted to T-scores, and then can be compared to a mean of 50 and standard deviation of 10. These subscales should take about 10 minutes to complete. A score of 70 or higher on the PROMIS Depression scale will result in the Adherence Study PI or an AI, or the study team member for the primary medical protocol to talk (by phone or in person) to the patient/caregiver about this and may necessitate a referral to an outside mental health professional.

3.2.4 Generic Medication Diary Form

To be completed by adult patients or caregivers of pediatric patients as the medication is taken and returned to primary study team at each clinical protocol re-staging visit (same visits at which the MEMS™ cap data will be retrieved). If the clinical trial on which the patient is enrolled has its own patient diary form, this can be used in place of the generic form provided in **Appendix G**.

3.2.5 Pill Count Form

This form is to be completed by the study team at the time of each clinical protocol re-staging visit (same visits at which the MEMS™ cap data will be retrieved).

3.2.6 Barriers to Adherence Questionnaire

The Barriers to Adherence Questionnaire includes a list of common reasons why people might miss a dose of medication. The respondent is asked to check any items that caused the patient to miss a dose of the NF study medication in the past month. The form will be sent electronically via a link to a secure site (Scribe) to patients when MEMS™ data show adherence to be less than 90%. The form will be sent as close in time as possible (ideally within one week and if feasible within one month) of the data being reported to the study team. At the end of the study, any patients who had not previously completed the Barriers to Adherence Questionnaire will be asked to do so. Reminders will be sent if patients do not respond within one week (phone and/or email). If participants do not complete the questionnaire after three prompts, we will document the noncompletion and these data will be used in consideration of feasibility. There is an adult

self-report version, a child self-report version (ages 8 and up) and a parent version (parents of children 3 – 17 years). These forms are in **Appendix F**.

3.2.7 MEMS™ Recording Form

This form allows adult patients or caregivers of pediatric patients to record any times at which MEMS™ bottle openings do not correspond to doses taken. For example, patients may indicate that they removed their AM and PM doses in the morning because they were not going to be home at the time of the PM dose. Adjustments to the MEMS data may be made in accordance with the data on this form. See **Appendix I**.

3.2.8 Adherence Interview

Patients ages 12 and older and parents of patients 3-18 years will be asked to complete an interview via phone or video chat with one of the study investigators ideally between cycles 8 and 12 or at the time of coming off study (whichever is later). The qualitative interview will be recorded and transcribed in order to conduct content analysis, which may inform future adherence interventions. We will attempt to conduct interviews with everyone, with a goal of interviewing 80% of adult participants, 80% of participants 12-17, and 80% of parent participants. The interview contains 6 questions about barriers and facilitators to adherence and preferences for adherence interventions, and is expected to take between 15-30 minutes. See **Appendix J** and **Appendix K**.

3.3 STUDY CALENDAR

Procedure	Baseline	Routine Treatment Protocol Re-Staging Visits	Other Timepoint	After 18 Cycles of treatment or at time patient is off treatment trial
Demographic Form	X			
Life Events Checklist	X			
NF1 QOL Questionnaires (PROMIS)	X			
Medication Diary[1]		X		
Pill Count Form[2]		X		
MEMS Record Form[3]			X[3]	
Barriers to Adherence Questionnaire[4]			X[4]	X
Adherence Interview[5]			X[5]	

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[1]To be completed by the patient and/or caregiver. Can use the Generic Medication Diary Form (**Appendix G**) or treatment protocol specific diary form

[2] To be completed by the study team at the time of routine protocol re-staging visit (**Appendix K**)

[3] Will be given to patients/caregivers at baseline to complete only when pill bottle openings do not correspond to medication taking (**Appendix I**).

[4] Will be sent electronically to any subject who has < 90% medication adherence documented by MEMS™ systems (**Appendix F**). This questionnaire may be sent to a single subject more than once (each time adherence < 90% is identified). All patients will be sent the questionnaire after 18 cycles of treatment or at the time patient comes off treatment trial (whichever comes first).

[5] To be performed with primary caregiver of patients 3-18 and patients ages 18+ any time between cycles 8 and 12.

3.4 COMPENSATION

After 12 cycles or when taken off treatment (whichever is earlier), participants will receive a small amount of money ($25) to thank them for their time. Funds will be distributed in accordance with the Clinical Center's Research Volunteer system, such that participants can have the money directly deposited to a bank account or have a check mailed to them. If patients are taken off-study early (i.e., due to disease progression), we will still provide them with $25 as long as they have completed the Barriers to Adherence questionnaire and phone interview (since the payment is offered to thank them for their time doing the questionnaire). They will also be paid an addition $15 for completing the telephone interview as described above.

Based on the HRPP SOP Appendix B, participants will be compensated for completion of questionnaires (1.5 units = $15) + Behavioral Tasks (using electronic monitoring caps and returning it to clinic; 1 unit = $10) = $25. Participants will be paid separately for a telephone interview (1.5 units = $15).

3.5 OFF STUDY CRITERIA

Participants will be removed from this study for any of the following:

- Completion of protocol requirements (18 cycles of therapy completed and final questionnaire completed)
- Patient comes off treatment on the concurrently enrolled clinical trial for treatment of plexiform neurofibroma(s)
- Participant requests to be withdrawn from study
- Patient develops significant cognitive or emotional difficulties that would prevent them from being able to understand and/or participate fully in the study or complete the measures.
- Lost to follow up
- Investigator discretion
- Death
- If the patient meets an off-study criterion, then the adult/caregiver of that patient should also be removed from the protocol.

4 DATA COLLECTION AND EVALUATION

4.1 DATA COLLECTION

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system (Labmatrix and/or Excel) and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

Adverse events occurring as a result of treatment for the underlying condition or medical treatment for pain will NOT be recorded on this study.

End of study procedures: Data will be stored according to HHS, FDA regulations, and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, this will be reported expeditiously per requirements in section **5.2.1**.

4.2 Data Sharing Plan

I will share coded, linked or identified data with approved outside collaborators under appropriate agreements; and coded, linked data will be shared at the time of publication and or public presentation.

5 NIH REPORTING REQUIREMENTS / DATA AND SAFETY MONITORING PLAN

5.1 Definitions

- Please refer to definitions provided in Policy 801: Reporting Research Events found here.

5.2 OHSRP Office of Compliance and Training / IRB Reporting

5.2.1 Expedited Reporting

Please refer to the reporting requirements in Policy 801: Reporting Research Events and Policy 802 Non-Compliance Human Subjects Research found here.

5.2.2 IRB Requirements for PI Reporting of Adverse Events at Continuing Review

Please refer to the reporting requirements in Policy 801: Reporting Research Events found here.

5.3 NCI Clinical Director Reporting

Problems expeditiously reported to the OHSRP in iRIS will also be reported to the NCI Clinical Director. A separate submission is not necessary as reports in iRIS will be available to the Clinical Director.

In addition to those reports, all deaths that occur within 30 days after receiving a research intervention should be reported via email to the Clinical Director unless they are due to progressive disease.

To report these deaths, please send an email describing the circumstances of the death to Dr. Dahut at NCICCRQA@mail.nih.gov within one business day of learning of the death.

5.4 NIH Required Data and Safety Monitoring Plan

5.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis to ensure that study implementation and follow up data collection are organized and completed in a timely fashion. The principal investigator and/or AI will review all data within one week of submission. Events meeting requirements for expedited reporting as described in section **5.2.1** will be submitted within the appropriate timelines.

The principal investigator and lead AI will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

6 STATISTICAL CONSIDERATIONS

6.1 PRIMARY ENDPOINT

The primary endpoint is to determine the proportion of enrolled patients for which we can collect data from the MEMS™ system for two or more cycles of treatment. It would be desirable and the MEMS system considered feasible in this setting if this were to equal or exceeds 75%.

6.2 SECONDARY ENDPOINTS

6.2.1 Average percent adherence based on the MEMS™ data only for cycles 1-4, 5-8, 9-12 and 13-18

6.2.2 Relationships between adherence (correlations, t-tests, etc.) and demographics, life events and barriers to adherence will be used to identify patient characteristics that may predispose to poor medication adherence

6.3 EXPLORATORY ENDPOINTS

6.3.1 Average adherence rates calculated from the pill counts, patient diaries and MEMS™ caps will be compared

6.3.2 Response to therapy will be defined as either a partial or complete response as per the primary clinical trial on which they are being treated. Response rates will be compared between patients that are adherent to medication (≥90% adherence by MEMS™) with patients that are non-adherent to medication (<90% adherence by MEMS™)

6.3.3 Average adherence rate (based on MEMS™ data) for patients ≤ 12 and those > 12 years old. Propose to use twelve years old as a cut-off point since adherence often declines during adolescence

Qualitative analysis of data from adherence interviews to determine needs of patients on NF clinical trials to improve adherence

6.4 ANALYSIS OF THE PRIMARY ENDPOINT

We will calculate the proportion of patients enrolled on this study who have at least two full cycles of medication adherence data recorded (considered a 'success' with respect to feasibility). The fraction along with 80% and 95% confidence intervals will be reported. We will also plan to use descriptive statistics to report the median number of cycles monitored for all patients.

6.5 ANALYSIS OF THE SECONDARY ENDPOINTS

The first secondary objective is to evaluate medication adherence over time in patients with NF1 receiving oral medications for treatment of plexiform neurofibroma(s) on a clinical trial. The reported results using the MEMSTM data will also be compared to that obtained via pill counts and patient diaries. Patients assigned drug holds by the study team that cover more than 50% of originally prescribed doses within any consecutive 3 months may be excluded from analyses that examine patterns of adherence over time. We may do separate exploratory analyses looking at longitudinal adherence among those with extensive drug holds depending on how many patients constitute this group by the end of the study.

As an additional secondary objective, we will determine the factors (demographics, QOL, etc) related to adherence. To do this, we will conduct bivariate correlations or analysis of variance between MEMS

adherence rates and demographics, PROMIS t-scores, and barriers most frequently endorsed on the barriers questionnaire.

6.6 Analysis of Exploratory Endpoints

Patients who are enrolled onto this trial will have the fraction of the total times that their medication is intended to be taken determined and reported with descriptive statistics based on results obtained using the MEMSTM system. This will be determined per patient as a percentage of the total planned medication administrations during all doses for which the patient is enrolled on the trial and eligible to be receiving medication. All study team directed medication holds and/or dose changes will be documented on the Pill Count Form (**Appendix H**) and will be used to determine the total planned medication adminstrations.

For each patient, there will be a percentage of total planned medication administrations calculated separately for cycles 1-4, cycles, 5-8, cycles 9-12 and cycles 13-18. Despite the limited number of patients to be enrolled, paired difference in the percentages between cycles 1-4 vs. 5-8, cycles 9-12 vs. 13-18, and cycles 1-4 vs. 9-12 will be formed for all patients during all evaluable cycles and reported using descriptive statistics. The calculated differences in adherence rates between time points will also be tested for being equal to zero using a Wilcoxon signed rank test, and interpreted as exploratory because of the limited amount of data.

The adherence rates as determined by the pill counts and the patient diaries will be recorded, and the agreement between these two measures and the MEMSTM percentages will be evaluated using exploratory and descriptive statistical methods. For example, the difference between two measures reporting the fraction of intended doses for a given set of three cycles will be reported and may be displayed graphically or formally tested using a paired analysis.

The analyses for all other secondary and exploratory objectives will be descriptive. Graphical presentations, such as histograms, stem and leaf plots, and scatterplots may be generated as appropriate to the type of endpoint.

- Transcriptions of individual interview will be created and analyzed descriptively using NVivo software.
- We will calculate and describe the percent medication adherence as documented by pill count, patient diary and using the MEMSTM system

6.7 Sample size determination

The primary objective of this study is to establish the feasibility of using MEMSTM caps to monitor medication adherence in the NF1 population. Therefore, we will calculate the proportion of patients enrolled on this study who have at least two full cycles of medication adherence data recorded (considered a 'success' with respect to feasibility). With a total of 12 evaluable subjects, if the true probability of a success were 50%, then the probability of obtaining 9 or more of 12 patients who have a success would be 7.3%. If the true probability of success were 85%, the probability of obtaining 9 or more of 12 who have a success would be 90.8%. Thus, observing 9 or more out of 12 patients (75%) who have a success is the goal and would result in considering the MEMS procedure to be sufficiently feasible for further consideration.

It is expected that 1 subject per month may enroll on this study. In order to allow for a small number of inevaluable subjects, the accrual ceiling will be set at 15 subjects and 15 caregivers/parents. It is expected that accrual of up to 15 subjects may be accrued within 1.5 years.

6.8 Subject Accrual

We anticipate accrual of approximately 12-15 patients.

7 HUMAN SUBJECTS PROTECTIONS

7.1 RATIONALE FOR SUBJECT SELECTION

Neurofibromatosis type 1 is a genetic disorder with a worldwide incidence of 1:3500 individuals. No groups, in regard to gender, race or ethnicity, are being excluded from participation in the trial.

Children under the age of 3 and adult patients (not parents or caregivers) older than 59 are being excluded because the children < 3 are unlikely to be able to swallow pills and therefore we cannot easily track their medication adherence. We are excluding subjects > 59 years old as the medication taking routines of older patients may vary from younger ones (may have more medications to take, etc.) and the target population for any future intervention will likely be children/young adults. Parents/caregivers may be any age.

Non-English speaking participants will not be included because at this initial level of measure validation, it is important to create a reliable and valid measure in English before it is put through the necessary rigorous translation process to create versions in other languages. A finalized measure will not be available until after phase 2; thus, it will be available for translation into other languages after the current study has been completed.

7.2 PARTICIPATION OF CHILDREN

The purpose of this study is to establish the feasibility of using MEMS™ to monitor medication adherence for individuals with NF1 and PNs. Therefore, children will be entered onto this research trial. Pediatric specialists who have extensive experience in performing work with children participating in clinical trials will conduct the trial.

7.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adult subjects unable to give consent are excluded from enrolling in the protocol. All subjects must be able to understand and/or participate fully in the study or complete the study measures. Should the subject become decisionally impaired during participation he/she will be removed from study as there is no prospect of direct benefit to them.

7.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

As this is a behavioral monitoring study, no medical treatments will be administered and therefore the risks are considered minimal. The completion of the primary questionnaires (background form, life events checklist, and PROMIS forms) requires a maximum of 18-20 minutes at baseline and follow-up time points. The adherence interviews are expected to take between 15 and 30 minutes. Although we do not anticipate this, one potential risk of participation is significantly increased levels of anxiety or stress related to discussions of medication adherence. If this occurs, a psychologist on the NCI research team will be available to discuss concerns with the patient and make appropriate follow-up recommendations, which may include referral to a local mental health provider.

There are no direct benefits anticipated from participation in the study.

7.5 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

The informed consent document will be provided to the participant or consent designee(s) (e.g., the parent/guardian if participant is a minor) for review prior to consenting. A designated study investigator will carefully explain the procedures and tests involved in this study, and the associated risks, discomforts and benefits. In order to minimize potential coercion, as much time as is needed to review the document will be given, including an opportunity to discuss it with friends, family members and/or other advisors, and to ask

questions of any designated study investigator. A signed informed consent document will be obtained prior to entry onto the study.

The initial consent process as well as re-consent, when required, may take place in person or remotely (e.g., via telephone or other NIH approved remote platforms) per discretion of the designated study investigator and with the agreement of the participant/consent designee(s). Whether in person or remote, the privacy of the subject will be maintained. Consenting investigators (and participant/consent designee, when in person) will be located in a private area (e.g., clinic consult room). When consent is conducted remotely, the participant/consent designee will be informed of the private nature of the discussion and will be encouraged to relocate to a more private setting if needed..

Where deemed appropriate by the clinician and the child's parent(s) or guardian, the child will also be included in all discussions about the trial and age-appropriate language will be used to describe the procedures and tests involved in this study, along with the risks, discomforts and benefits of participation. The assent process will take place in conjunction with consent; therefore, in person and remote assent are permitted under the same circumstances as in person and remote consent. Verbal assent will be obtained as appropriate for children ages 10-11. Children under the age of 18, but who are age 12 or older will be asked to sign an age appropriate assent form. Children under the age of 10 will not be required to provide assent as they typically do not have the cognitive ability to fully understand the nature of research. The consent/assent process will be documented in the child's medical record, including the assessment of the child's ability to provide assent (verbal versus written) as applicable. All children will be contacted after they have reached the age of 18 to determine whether they wish to continue on the trial and informed consent will be obtained from them at that time.

7.5.1 Request for Waiver of Consent for Screening Activities

Prior to the subject signing the consent for this study pre-screening activities listed in section **2.2.1** may be performed.

We request a waiver of consent for these activities as they involve only minimal risk to the subjects. A waiver will not adversely affect the rights and welfare of the subjects given that the activities are only intended to determine suitability for screening for participation in research protocols. These activities could not practicably be carried out without the wavier as central recruiting services, utilized in the NIH Clinical Center, perform pre-screening activities for multiple studies and obtaining consent for each one is beyond their resources. The subjects will be provided with additional pertinent information after participation as they will be informed whether are not they are eligible to sign a consent for additional screening.

7.5.2 Consent for minors when they reach the age of majority

When a pediatric subject reaches age 18, continued participation (including ongoing interactions with the subject or continued analysis of identifiable data) will require consenting of the now adult with the standard protocol consent document to ensure legally effective informed consent has been obtained. We request waiver of informed consent for those individuals who have met an off-study criterion as defined in section **3.5**.

Requirements for Waiver of Consent consistent with 45 CFR 46.116 (d):

(1) The research involves no more than minimal risk to the subjects.

   a. Analysis data from this study involves no additional risks to subjects.

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects.

a. Retention of data does not affect the welfare of subjects.

(3) The research could not practicably be carried out without the waiver or alteration.

a. Considering the length of time between the minor's last contact with the research team and their age of majority, it will likely be very difficult to locate them again. A significant reduction in the number of data analyzed is likely to impact the quality of the research.

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

a. We do not anticipate that any information generated by these studies would be pertinent in any way to the health and treatment of these research subjects. However, if such information is generated, and we are able to locate the research subject(s), we would provide the information to them. The subjects who provide the data will not be contacted by anyone connected with the research without prior approval by the IRB.

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