BCH protocol

TITLE: Pilot Study of Metformin for Patients with Fanconi Anemia

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ABSTRACT AND SCHEMA

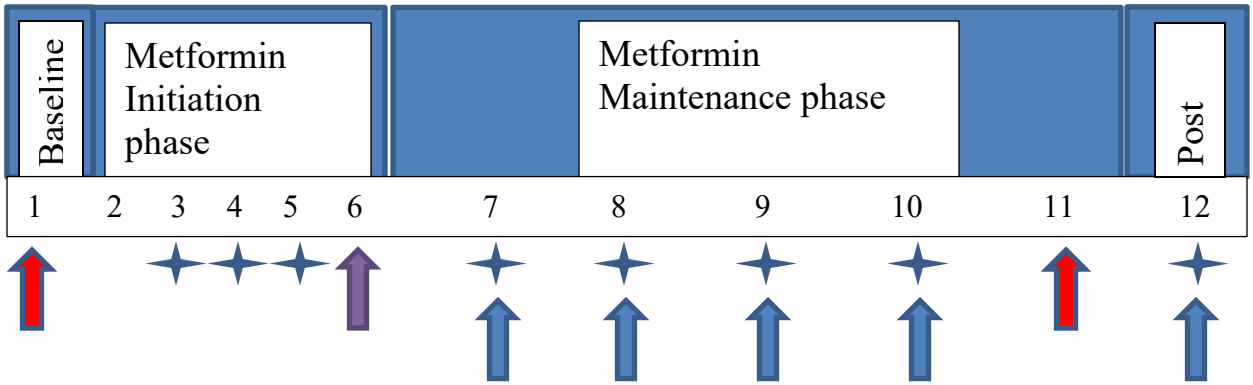
Fanconi Anemia (FA) is an inherited bone marrow failure disorder characterized by a DNA repair defect leading to exhaustion of hematopoietic progenitor cells manifesting as cytopenias with a predisposition to develop hematologic malignancies and head and neck squamous cell carcinomas. Some patients with FA also have congenital anomalies.[1] Studies have demonstrated that Fanconi Anemia patients have defects in homologous end joining and DNA repair and that this DNA repair defect is partially mediated by both endogenous and exogenous aldehyde toxicity.[2-6]

Allogeneic hematopoietic stem cell transplantation is curative for hematologic complications of FA, though it cannot abrogate the increased risk of solid tumors. However, transplant is associated with many complications including GVHD and may increase the risk of subsequent solid tumors, not all patients are candidates for transplant due to medical co-morbidities, and some may not have suitable donors.[7,8]

Aside from hematopoietic stem cell transplantation, there are very few medical therapies that have been shown to improve hematopoiesis and peripheral blood counts in patients with Fanconi Anemia who have developed aplastic anemia or even mild cytopenias. While androgens can ameliorate cytopenias in patients with FA, only a subset of patients have a hematologic response, and long-term treatments are limited by side effects (transaminitis, virilization, risk of developing hepatic adenomas and carcinomas) as well as waning hematologic responses over time.[9] Safe and effective oral agents to treat the cytopenias are urgently needed for patients with FA.

Metformin (N,N-dimethylbiguianide) has been used widely for many decades and has a well-characterized side effect profile. Initially this drug was developed for type II diabetes and insulin resistance; however, there has been recent renewed interest in Metformin given its anti-oxidant effects and potential protective effects, as observational studies have demonstrated a decreased incidence of breast cancer, lung cancer, colorectal cancer, and hepatocellular carcinoma in patients treated with Metformin, possibly through AMP-kinase activation and mTOR inhibition (summarized in [10]). Relevant to this study, Metformin has also demonstrated aldehyde scavenging capabilities. Recent preclinical models both in FA cell lines and in FA mice have demonstrated that Metformin improved the platelet count and ANC in FA mice and that this may be mediated by increasing the percentage of cells in quiescence and by improving DNA repair, as Metformin treated fibroblast cells had decreased numbers of spontaneous radials and breakage.[11]

Based on these data, we propose a single institution, open-label, single arm pilot study of Metformin in patients with Fanconi Anemia and cytopenias with the primary endpoint of hematologic response. This study will also assess safety, tolerability, and the biologic effects of Metformin in patients with FA.



Clinic visit, labs, and marrow evaluation

Clinic visit, labs, and PK samples (when available); otherwise, phone call and local labs

Local labs

Phone call and drug diary review

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2 BACKGROUND

2.1 Fanconi Anemia

Fanconi Anemia (FA) is an inherited bone marrow failure disorder characterized by a DNA repair defect. FA patients have a high risk of developing aplastic anemia and have a predisposition to develop malignancies including MDS, AML, and solid tumors, namely squamous cell carcinomas of the head, neck, GI tract, and vulva. Many patients have congenital anomalies including renal abnormalities, skeletal dysplasias, and skin abnormalities. Allogeneic hematopoietic stem cell transplantation can cure the hematologic complications of FA; however, patients who undergo stem cell transplantation may have an increased risk of developing solid tumors due to the effects of chemotherapy and radiation used in transplant conditioning regimens as well as the effects of inflammation from mucosal damage and from GVHD.[1] Donor availability also limits transplant options for a subset of patients.

For patients unable or unwilling to undergo a hematopoietic stem cell transplant, androgens such as oxymethalone or danazol can improve blood counts in many patients with FA, though a subset of patients fail to respond or relapse after an initial response. Patients on androgens remain at risk for leukemia. Androgens are associated with significant side effects including transaminitis, cholestasis, peliosis hepatis, hepatic adenomas and carcinomas, and virilization. Hepatic complications of androgens may increase the risk of a subsequent hematopoietic stem cell transplant. Safe oral agents to treat bone marrow failure without increasing the risk of malignancy and to target the underlying DNA repair defect are urgently needed.

In recent years, intensive scientific laboratory research by a collaborative group of leading FA investigators has identified potential agents, including Metformin and TGF-β inhibitors, that improve hematopoiesis in vitro and in animal models while providing protection from DNA damage. These promising preclinical findings need to be studied in clinical trials to develop new treatments for FA patients.

2.2 Metformin

Metformin (N,N-dimethylbiguianide) is an FDA approved drug with a well-characterized side effect profile with low toxicity. Metformin was initially developed as a drug for type II diabetes and insulin resistance. There has been recent renewed interest in Metformin given its anti-oxidant effects, and Metformin has been demonstrated to decrease the incidence of certain types of solid tumors in patients taking this medication in observational studies. It has been hypothesized that these anti-cancer properties may be due to AMP-kinase activation and mTOR inhibition.[6–9,10] In addition, 39% of patients with FA on screening had glucose and insulin handling abnormalities, making Metformin an attractive drug for this patient population as Metformin may improve both hematopoiesis and insulin resistance in this population.[10] Although there have been rare instances of lactic acidosis with Metformin treatment, a Cochrane review from 2010 demonstrated that there were no cases of lactic acidosis from 347 comparative trials and cohort studies representing 70,490 patient-years of Metformin use.[25]

2.2.1 Preclinical pharmacology and toxicity studies of Metformin

Carcinogenesis and Mutagenesis studies:

Long-term carcinogenicity studies have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with Metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with Metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day. There was no evidence of a mutagenic potential of Metformin in the following in vitro tests: Ames test (S. typhimurium), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the in vivo mouse micronucleus test were also negative. Fertility of male or female rats was unaffected by Metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons (Metformin label).

Pregnancy: Pregnancy Category B.

Nursing mothers: Studies in lactating rats show that Metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers (Metformin Label).

2.2.2 Prior clinical experience with Metformin

Pediatric studies for obesity are included in a meta-analysis of 5 studies which demonstrated that Metformin treatment led to a decrease in BMI by a mean of 1.42kg/m2 over placebo treatment. This meta-analysis did not demonstrate strong evidence of a treatment effect on fasting glucose. There most common side effect was gastrointestinal (20-30%) and was more common in the treatment Metformin group as compared to the placebo groups (risk difference of 10-14%).[12]

Another systematic review and meta-analysis of 9 randomized controlled trials for obesity in adolescents aged 12 to 19 on Metformin doses of 1000mg to 2000mg daily did not demonstrate a statistically significant difference in frequency of gastrointestinal adverse events in the Metformin group as compared to the placebo group.[13] This study also demonstrated a mean decrease in BMI by 1.42mg/m2 in the treatment group as compared to the placebo control group, and demonstrated decrease in hyperinsulinemia (-9.9uU/mL) in the treatment group as compared to the control group.

A recent systematic review details the studies of Metformin in obese non-diabetic children and adolescents.[14] A number of studies included in this review have documented the safety and tolerability of Metformin below 10 years of age.[15-19] None of these studies demonstrated any change in the adverse effect profile when compared to patients older than the age of 10. The

most common side effects as in older patients were gastrointestinal side effects.

Metformin has also been studied in a population of patients aged 6 to 17 years with weight gain associated with atypical antipsychotic medications, with doses of 500mg BID for children up to age 10 and 850mg BID for patients 10 to 17 years of age. Metformin decreased BMI z scores by -0.1 in the treatment group as compared to the control group and overall was well tolerated with 5 patients (out of 61 randomized patients) who discontinued treatment, 4 due to agitation and 1 due to sedation. Patients who received Metformin treatment had a nonsignificant higher incidence of gastrointestinal side effects, though these were experienced for significantly higher duration of treatment (25.1% versus 6.8%).[20]

Metformin has also been tested in patients down to the age of 4 in assessing changes in markers of insulin resistance and inflammation. It was well tolerated other than diarrhea in 35.7% of the patients during week 1, which disappeared in all cases but one, and no patients discontinued the drug due to side effects. No other serious adverse events were noted.[21]

Metformin has been tested in 10 non-diabetic pediatric patients with steatohepatitis with 500mg BID dosing for 24 weeks in a phase II clinical trial and demonstrated statistically significant improvement in AST and ALT, liver fat, and insulin sensitivity as well as quality of life. Although 3/10 patients developed gastrointestinal side effects, all subjects subsequently tolerated Metformin treatment without GI side effects by 4 weeks. There were no episodes of acidosis.[22]

Metformin has been demonstrated to decrease cancer risk in adult patients with type II diabetes in a population-based cohort study. Patients who had received more than 360 daily doses of Metformin monotherapy had a decrease in cancer risk by a hazard ratio of 0.4 [0.22-0.66], and patients who received more than 1080 defined daily doses of Metformin had a hazard ratio of 0.27 [0.09-0.84].[23]

2.3 Rationale for evaluation of Metformin in Fanconi Anemia

2.3.1 Preclinical activity of Metformin in Fanconi Anemia

Our collaborators at the Oregon Health Sciences University led by Dr. Markus Grompe extensively studied the effects of Metformin in an FA mouse model and in FA patient-derived cells and determined that Metformin administration both improves hematopoiesis and reduces DNA damage. Their data, which was recently published in Blood, is summarized below.[11]

In this study, FANCD2-/- mice were fed Metformin (roughly 65% of the maximum dose in humans, or 300mg/kg/day) for 6 months. Serial blood counts demonstrated improvement in platelet counts ($p < 0.05$), hemoglobin ($p < 0.005$), and WBC in the Metformin-treated mice.

Since marrow failure and cytopenias may be triggered or exacerbated by physiologic stress, the researchers tested whether Metformin could protect against hematologic abnormalities in mice treated with poly(I:C), which induces inflammation. Interestingly, Metformin provided some protection from the poly(I:C)-induced aplastic anemia when compared to treatment with placebo ($p<0.01$). Metformin-treated FANCD2-/- mice treated with poly(I:C) demonstrated preservation

of spleen colony formation (CFU-S) following transfer of bone marrow from these mice into irradiated recipients. In contrast, the FA mice exposed to poly(I:C) without Metformin had dramatically reduced ability to form CFU-S. This experiment suggests that the hematopoietic stem/progenitor cells are relatively preserved with Metformin treatment.

Prior data suggest that Metformin may have tumor-protective effects. To assess potential effects of Metformin on tumorigenesis, the cancer-prone FANCD2-/- Tp53+/- mice were treated with Metformin or placebo, and followed for tumor development and for survival. The FANCD2-/- Tp53+/- mice had a longer latency period until tumor formation (first tumors were found at 142 days as compared to 244 days) and longer tumor-free survival time (405 days as compared to 368 days), suggesting that Metformin delays tumor formation in FANCD2-/- Tp53+/- mice. This effect was not observed in the FANCD2+/+ Tp53+/- mice, suggesting that Metformin's effect on tumor formation in these mice might be specific to the FANCD2-/- mice.

The preclinical data generated by our colleagues at OHSU and described above suggest that Metformin treatment of FA cell lines *in vitro* and FA mice *in vivo* improves hematopoiesis both at baseline and when stressed with poly(I:C) administration and may do so through improvement in aldehyde handling, decreased chromosomal breakage and radial formation, and increased quiescence. FA mice have a modest improvement in tumor free survival with a Metformin diet as compared to a placebo diet.

2.4 Rationale for planned correlative studies

The mechanisms causing bone marrow failure in patients with Fanconi Anemia have largely been studied in murine models and patient-derived cells in vitro. Biomarkers of marrow failure in Fanconi Anemia have not been well studied, and a descriptive study of biomarkers associated with treatment response may advance our understanding of marrow failure in these patients. Although the basic science understanding of Fanconi Anemia has progressed rapidly over the past decade, the clinical treatment options have not progressed at the same rate.

The mechanisms promoting bone marrow failure in FA have been postulated to include aldehyde-mediated toxicity, stem cell exhaustion, and DNA damage. The preclinical data with Metformin suggests that Metformin may be improving hematopoiesis in FA mice and cell lines by protecting against aldehyde-mediated toxicity, promotion of stem cell quiescence, and reduction of DNA damage.[11]

1) Both guanine derivatives of aminoguanidine and Metformin were able to protect FA-G patient derived lymphoblastoid cells from exogenous formaldehyde and MMC toxicity. A similar experiment in which endogenous formaldehyde levels were increased by administering a small molecule inhibitor of Adh5 also demonstrated similar results in which FA-A derived fibroblast cells were protected from chromosomal breaks and radial formation by administration of Metformin ($p<0.0001$ and $p<0.001$).

2) Metformin induced cell cycle quiescence of the HSC compartment in FANCD2-/- mice as compared to control mice. It is hypothesized that quiescence of stem cells may decrease the harmful effects of poly(I:C) induced cycling of HSCs.

3) FA patient cells demonstrate high rates of radial chromosome formation and chromosomal breaks, and treating FA-A patient derived fibroblast cells demonstrated decreased radial and chromosomal breakage formation when treated with Metformin as compared to placebo. Another guanidine derivative, aminoguanidine, was also tested and shown to have a similar effect.

Therefore, correlative studies will describe whether Metformin changes the quiescence of hematopoietic stem cells, leads to a change in the expression of genes in the DNA damage pathway, alters the chromosomal breakage test results after treatment with MMC or DEB, affects the formation of micronuclei in a buccal cell assay, and alters patients' aldehyde handling.

2.5 Overall summary of rationale

Since Fanconi Anemia is a rare disease, a small prospective pilot study was chosen as the study design. Although the small sample size and open-label single-treatment arm design of this study will not be able to definitively determine clinical benefit of Metformin treatment in this patient population, this study will provide additional information regarding safety, tolerability, and preliminary efficacy of Metformin in FA patients and may provide the basis for a larger controlled clinical trial.

As Metformin would be used as a chronic medicine if it improves hematopoiesis, it is necessary to assess safety and tolerability of this medicine over several months. As our goal is to improve the understanding of the mechanisms by which Metformin may improve hematopoiesis, biological correlative studies will be integrated into the clinical trial with blood and marrow collection and analysis and may lead to additional hypotheses, which can in turn become the bases for additional potential therapies in this patient population.

There is urgency to run this trial since Metformin is available for clinical use and could easily be given off-study, in which case safety and efficacy will remain unclear, and there is a high unmet medical need for safe and tolerable medical therapies for patients with FA and marrow failure as there are no established treatment options for marrow failure other than bone marrow transplantation, androgen therapy, or hematopoietic growth factor therapy. Metformin is anticipated to be safe and tolerable in this patient population given the prior published clinical experience using this medication in various patient population including pediatric patients with type I and II diabetes and obesity, and Metformin is currently being used in trials for advanced solid tumors. The doses tested in this trial are doses which have either been FDA approved (ages 10 years and older), or doses which have been previously tested and well tolerated (ages 6-10 years).

3 PARTICIPANT SELECTION

3.1 Inclusion Criteria

3.1.1 Age ≥ 6 years and ≤ 35 years

3.1.2 Lansky/Karnofsky performance status ≥ 50% for patients ≥16 years of age and Lansky ≥ 50% for patients <16 years of age (see Appendix A)

3.1.3 Diagnosis requirement

3.1.3.1 Participants must have a clinical diagnosis of Fanconi Anemia.

3.1.3.2 Participants must have confirmed DEB/MMC testing to document diagnosis of Fanconi Anemia.

3.1.4 Patients must have at least one of the following cytopenias:

- Hemoglobin <10g/dL
- Platelets <100k/uL
- Absolute neutrophil count <1000/uL

3.1.5 Participants must have normal organ function as defined below:

3.1.5.1 Hepatic Function

- Total bilirubin ≤ 1.5 x upper limit of normal for age
- ALT/AST ≤ 135 U/L

3.1.5.2 Renal Function

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

AND

- Creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal

3.1.5.3 Normal cardiac status as documented clinically, otherwise they will need an echocardiogram prior to enrollment

3.1.5.4 Serum bicarbonate must be >17.

3.1.5.5 Participants of child-bearing or child-fathering potential must agree to use adequate contraception (hormonal birth control; intrauterine device; double barrier method; or total abstinence) throughout their participation, including up until 30 days after last dose of Metformin.

3.1.6 Ability to understand and/or the willingness of the patient (or parent or legally authorized representative, if minor) to provide informed consent, documented using an institutionally approved informed consent procedure

3.2 Exclusion Criteria

3.2.1 Patients must not have undergone prior bone marrow transplantation.

3.2.2 Patients must not have very severe aplastic anemia at the time of enrollment which would require bone marrow transplantation (as defined by at least 2 out of the following 3: ANC <200/uL, platelets <20k/uL, absolute reticulocyte count <40k/uL). If patients are not eligible for a transplant and otherwise meet the inclusion/exclusion criteria, then they may enroll in this trial.

3.2.3 Patients must not be taking any other concurrent medications to improve their hematopoiesis such as androgens or growth factors such as G-CSF, EPO, or TPO mimetics. If any of these prior therapies, including androgens, have been taken, the patient must wait 30 days before enrolling.

3.2.4 Pregnant participants will not be entered on this study given that the effects of Metformin on the developing human fetus are unknown.

3.2.5 Breastfeeding mothers are not eligible because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Metformin.

3.2.6 Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to Metformin.

3.2.7 Patients must not have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Patients must not have prior history of symptomatic hypoglycemia over the past year or hypoglycemia with glucose <50mg/dL on screening and baseline laboratory assessments.

3.2.9 Patients must not have type 1 diabetes mellitus.

3.2.10 Patients must abstain from alcohol as part of this study.

3.2.11 Patients must not have a diagnosis of myelodysplastic syndrome or leukemia, or other concurrent malignancy undergoing treatment.

3.2.12 Patients must not have vitamin B12 deficiency.

3.2.13 Patients must not have G6PD deficiency.

3.3 Inclusion of Children and Minorities

Both male and female children of all races and ethnic groups are eligible for this trial.

4 ENROLLMENT PROCEDURES

4.1 General Guidelines

Eligibility screening: Available laboratory test results which are standard of care, such as CBC with differential, chemistries, LFTs, and prior bone marrow aspirate/biopsies, will be carefully reviewed to determine the participant's eligibility for the study prior to the patient signing consent (see section 3).

Baseline Assessments: Following the patient's consent, baseline laboratory assessments will be drawn and are detailed in Section 5.3 (study visit procedures) and section 5.7 (schedule of assessments). An investigator will confirm eligibility criteria and will complete and sign the protocol-specific eligibility checklist. If patients no longer meet eligibility criteria based on their baseline assessments, they will be considered screen failures. If one of these patients later meets eligibility criteria, the patient can be re-screened for enrollment. In these instances, the baseline and eligibility tests would need to be repeated except for G6PD.

Following enrollment, participants may begin protocol therapy and should begin protocol therapy within 14 days. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). Specific baseline laboratory tests including CBC with differential, chem 10, and LFTs must be repeated prior to dosing on Day 1 if obtained >14 days prior to Day 1. The rest of the Day 1 assessments are detailed in Section 5.3 (study visit procedures) and section 5.7 (schedule of assessments).

4.2 Evaluable Patients

Patients will be deemed evaluable for hematologic response if they receive Metformin for at least one month in duration or if they receive Metformin for any duration of time and discontinue therapy for reasons related to study drug.

5 TREATMENT PLAN

5.1 Treatment Regimen

5.1.1 Pharmaceutical

Generic name: Metformin
Supply: Commercially available, generic
Route of administration: Oral
Pharmacology: Metformin is a biguanide derivative and is approved as an adjunct to diet and exercise to improve glycemic control in adults and children with type 2 diabetes mellitus
Product formulation: Metformin 500mg immediate release tablets and Riomet (Metformin HCl oral solution) 500mg/5mL liquid will be utilized for this study
Storage: Tablets should be stored at room temperature, 20-25°C, excursions permitted to 15-30°C; liquid should be stored at controlled room temperature 15-30°C (59-86°F)

5.1.2 Overview of Treatment Regimen

Patients may begin therapy on any day of the week. Each dose of Metformin will be recorded in a medication diary by patients ≥age 18, and by parents of patients <age 18. The medication diary will be returned to clinic staff at the end of each month. Dose modifications are described in Section 7.2. Reported adverse events and potential risks are described in Section 7. No investigational or commercial agents or therapies other than Metformin may be administered with the intent to treat the participant's cytopenias. Participants may continue to receive Metformin for up to 6 months unless they satisfy the criteria for removal from protocol therapy (see Section 5.5).

To minimize the risk of gastrointestinal upset, patients will increase the dose of Metformin over 4 weeks as follows.

For patients ≥10 years of age:

Initiation Phase:
Metformin will be initiated at a dose of 500mg/day, increased by 500mg/day once a week up to 2000mg/day.

Timepoint	Dose
Week 1	500mg qPM
Week 2	500mg BID
Week 3	500mg qAM, 1000mg qPM
Week 4 through end of treatment	1000mg BID

Maintenance phase: Patients will continue on the maximum dose of 1000mg BID or otherwise maximum tolerated dose for 6 months total duration.

For patients ≥6 years of age and <10 years of age:

Initiation phase:

Metformin will be administered at a dose of 500mg/day and increased by 500mg/day once a week up to 1000mg/day.

Timepoint	Dose
Week 1	500mg qPM
Week 2 through end of treatment	500mg BID

Maintenance phase: Patients will continue on the maximum dose of 500mg BID or otherwise maximum tolerated dose for 6 months total duration.

Dose Modification:
For patients who have difficulty tolerating Metformin at any point during the initiation or maintenance phases due to gastrointestinal upset or other AEs specified in section 7, the dose will be decreased by 500mg/day until a tolerated dose is achieved.

Dose interruption:
Patients must hold Metformin if they are NPO for any reason, have a period of prolonged fast more than 8 hours, a critical illness requiring IV fluids, and/or a gastrointestinal illness. The medication will be held until patient resumes regular PO intake.

Patients must hold Metformin for 24 hours prior to imaging scans which require contrast, such as CT scans. Patients may resume Metformin 24 hours after the completion of the contrast administration.

Dose interruptions will typically occur for no more than 7 days and will be monitored.

5.2 Agent Administration

Metformin is administered orally with food either once or twice daily as specified per dose level.

Metformin is supplied as a 500mg pill and a 500mg/5mL liquid.

Metformin is to be taken with meals (±30 minutes) to minimize GI upset. If a participant vomits a dose, the dose will not be repeated.

Each dose of Metformin will be recorded in a medication diary by a parent if patient age <18 years of age, or by the patient if ≥18 years of age. The medication diary will be returned to clinic staff at the end of month.

5.3 Study Visit Procedures

A total of 12 visits will be required in this study. Some visits are in person at Boston Children's Hospital, and some visits will be conducted over the phone with parents if <age 18 or with the patient if ≥18 years of age.

Visits 1 and 11 must be performed at the study site (Boston Children's Hospital). For patients

who are able to travel to Boston Children's Hospital for visit 6, pharmacokinetic studies will be performed. After initiation of study drug and prior to the end of therapy visit, subjects will be followed by their home physician or at Boston Children's Hospital and have blood work performed locally for interim visits as detailed below. The research team will contact the family for the interim phone calls as specified for visits 3, 4, 5, 7, 8, 9, 10, 12 to review drug diaries and adverse events and confirm laboratory assessments to be performed.

5.3.1 Visit 1: Baseline laboratory assessments – *BCH visit* (Day -28 to -1)
- Obtain informed consent
- Medical history
- Physical examination
- Lansky/Karnofsky Performance Status
- Height and weight
- Vital Signs
- Laboratory assessments: hematology (CBC with differential and reticulocyte count), chemistry (chem 10, LFTs), vitamin B12, G6PD, blood glucose, insulin level, oral glucose tolerance test, IGFBP-1, chromosomal breakage test, iron studies, hemoglobin electrophoresis
- Urinalysis
- Serum or urine pregnancy test
- Biomarker: bone marrow aspirate/biopsy
- Biomarker: aldehyde analyses
- Biomarker: buccal swab
- Distribution of drug diary

5.3.2 Visit 2: Initiation of therapy (Day 1)
- Drug administration: if the subject does not live locally and cannot pick up the study drug from BCH, drug will be shipped to the subject's home. Day 1 will be considered the day that the subject takes the study drug for the first time.

5.3.3 Visit 3 – *phone call* (Day 8 +/- 3 days)
- Drug diary review
- Adverse event assessment

5.3.4 Visit 4 – *phone call* (Day 15 +/- 3 days)
- Drug diary review
- Adverse event assessment

5.3.5 Visit 5 – *phone call* (Day 22 +/- 3 days)
- Drug diary review
- Adverse event assessment

5.3.6 Visit 6 – *phone call and local labs or BCH visit* (Day 29 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count), chemistry (chem 10, LFTs), blood glucose, insulin level. Subjects able to travel to BCH for this visit will return to outpatient blood drawing at BCH and will also have pharmacokinetic assessments performed at this time. Subjects unable to travel to BCH for this visit will have their blood drawn at their primary clinician or an outside lab, and the report will be sent to BCH. An in-person study visit is not needed at this time point.
- Pharmacokinetic assessments: Will be performed for local patients at 0, 1, 2, 4, 6

hours post dose
- Drug diary review
- Adverse event assessment

5.3.7 Visit 7 – *phone call and local labs* (Day 57 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count)
- Drug diary review
- Adverse event assessment

5.3.8 Visit 8 – *phone call and local labs* (Day 85 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count), chemistry (chem 10, LFTs), blood glucose, insulin level
- Urinalysis
- Urine pregnancy test
- Drug diary review
- Adverse event assessment

5.3.9 Visit 9 – *phone call and local labs* (Day 113 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count)
- Drug diary review
- Adverse event assessment

5.3.10 Visit 10 – *phone call and local labs* (Day 141 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count)
- Drug diary review
- Adverse event assessment

5.3.11 Visit 11: End of study treatment – *BCH visit* (Day 169 +/- 14 days)
- Physical examination
- Lansky/Karnofsky Performance Status
- Height and weight
- Vital Signs
- Laboratory assessments: hematology (CBC with differential and reticulocyte count), chemistry (chem 10, LFTs), vitamin B12, blood glucose, insulin level, oral glucose tolerance test, IGFBP-1, chromosomal breakage test, iron studies, hemoglobin electrophoresis
- Urinalysis
- Urine pregnancy test
- Biomarker: bone marrow aspirate/biopsy
- Biomarker: aldehyde analyses
- Biomarker: buccal swab
- Drug diary review
- Adverse event assessment

5.3.12 Visit 12 – *phone call and local labs* (Day 197 +/- 7 days)
- Laboratory assessments: hematology (CBC with differential and reticulocyte count)
- Adverse event assessment

Additional labs may be performed as clinically indicated.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Concomitant Medications

5.4.1.1 No other medication targeting hematopoiesis will be used concurrently, including androgens or hematopoietic stimulating agents such as EPO, G-CSF, or TPO agonists. The use of furosemide is contraindicated.

5.4.1.2 The following medications should be used with caution:

- Cationic drugs that are eliminated by renal tubular excretion should be used with caution (amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, and vancomycin).
- Other cationic transport-2 (OCT2)/multidrug and toxin extrusion (MATE) inhibitors include ranolazine, vandetanib, dolutegravir, and cimetidine.
- Carbonic anhydrase inhibitors, such as topiramate
- Nifedipine

5.4.1.3 Patients must not be on any anti-neoplastic agents during the duration of this study.

5.4.1.4 Appropriate antibiotics, blood products including transfusions, anti-emetics, fluids, electrolytes and general supportive care are to be used as clinically indicated.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression, and tolerance. Treatment may continue for up to 6 months from study entry and completion of planned follow-up, or until one of the following criteria applies:

- Diagnosis of myelodysplastic syndrome or leukemia
- Worsening of cytopenias as defined by one of the following, sustained over 8 weeks in duration:
  - Increase in transfusion requirement by two-fold
  - Decrease in hemoglobin by >1.5g/dL and absolute value <10g/dL
  - Platelet count <50% of baseline value and absolute value <100k
  - ANC <50% of baseline value and absolute value <1000
- Intercurrent illness that prevents further administration of treatment
- SAE or other toxicity that meets criteria for removal from protocol therapy (see Section 7)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Found to be ineligible, including participants who have repeat organ function laboratory at the baseline assessment which no longer meet eligibility criteria.
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Withdrawal of consent for treatment or treatment and data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy and the date the participant was removed must be documented in the case report form (CRF).

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI.

5.6 Duration of Follow Up

Participants will be followed for one month after study treatment is complete or until death, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Schedule of Assessments

Baseline disease assessments, such as bone marrow studies, must be performed within 28 days prior to starting study drug.

Study visits 2-5 should be within +/-3 days of, visits 6-10 and 12 should be within +/-7 days, and visit 11 should be performed within +/- 14 days of what is specified per protocol.

Visit Name	Screening										End of treatment	Follow up
Visit number	*1*	*2*$^{+}$	*3*	*4*	*5*	*6*	7	8	9	10	11	12

Day of cycle (+/-3 days unless otherwise indicated)	*-28 to -1*	*1*	*8*	*15*	*22*	*29 (+/-7 days)*	*57 (+/-7 days)*	*85 (+/-7 days)*	*113 (+/-7 days)*	*141 (+/-7 days)*	*169 (+/-14 days)*	*197 (+/-7 days)*
Obtain Informed Consent	X											
Demography	X											
Inclusion/exclusion criteria	X											
Relevant medical history/current medical conditions	X											
Diagnosis of Fanconi Anemia	X											
Prior therapies	X											
Concomitant medications	X											
Physical examination	X										X	
Lansky/Karnofsky Performance status	X										X	
Height	X										X	
Weight	X										X	
Vital signs	X										X	
Bloodwork	X					X	X	X	X	X	X	X
- Hematology (CBC with diff and retic)	X					X	X	X	X	X	X	X
- Chemistry (chem 10, LFTs)	X					X		X			X	
- Vitamin B12 level	X										X	
- G6PD	X											
- Blood glucose	X					X		X			X	
- Insulin level	X					X		X			X	
- Oral glucose tolerance test	X										X	
- IGFBP-1	X										X	
- Chromosomal breakage test	X										X	
- Iron studies (TIBC, serum iron, ferritin)	X										X	
- Aldehyde analyses	X										X	
- Hemoglobin electrophoresis	X										X	

Urinalysis (macroscopic)	X							X			X	
Serum or urine pregnancy test	X							X			X	
Drug dispensation		X										
Pharmacokinetic samples						X **						
Buccal swab sample for micronuclei assessment	X										X	
Bone marrow aspirate/biopsy	X										X	
- Aspirate for morphology	X										X	
- Biopsy	X										X	
- Karyotype	X										X	
- BMF/MDS FISH	X										X	
- Flow cytometry	X										X	
- CD34 HSPC cycling	X										X	
- Aldehyde analyses	X										X	
Drug diary/Drug administration		X										
Research team phone calls			X	X	X	X ***	X	X	X	X		X

+ Visit 2 is the day that the subject begins taking the study drug
** To be completed if study visit 6 occurs at BCH
*** To be completed if study visit 6 does not occur at BCH

6 HEMATOLOGIC RESPONSE CRITERIA

Hematologic improvement is based on modified MDS IWG criteria, which is listed below.[24] Improvement in counts should be sustained for at least two months and demonstrated by at least 2 consecutive measurements to be considered a hematologic response

Hematologic improvement	Response Criteria (responses must be sustained over a minimum of 8 weeks in duration)	
Erythroid response (pretreatment, <10g/dL)	Hgb increase by ≥1.5g/dL for non-transfusion dependent patients	For patients who are transfusion dependent: Transfusion independence Only transfusions given for Hgb ≤8g/dL or for symptoms will be counted in the response evaluation
Platelet response (pretreatment, <100k/uL)	If initially <20k/uL to start, then must increase to	If initially ≥20k/uL to start, then must have an absolute

	>20k/UL with an absolute increase of 100%	increase of >30k/UL
Neutrophil response (pretreatment <1000/uL)	If initially <500/uL to start, then must increase to >500/uL with an absolute increase of >250/uL	If initially ≥500/uL to start, then must have an absolute increase of >500/uL
Progression or relapse after HI*	At least one of the following: Decrease in ANC by >50% from baseline and absolute value <1000, platelet count decrease by >50% from baseline and absolute value <100k, reduction in Hgb by ≥1.5g/dL and absolute value <10g/dL, or doubling in transfusion requirement	

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Principal Investigator will submit reports of unexpected SAEs and other unanticipated problems to the Institutional Review Board (IRB) at Boston Children's Hospital and the Medical Monitor.

All serious adverse events regardless of attribution relative to study will be reported for review on an expedited basis. Unanticipated Problems which are related or possible related to study participation and which are:

1) non-serious AEs but which are unexpected (in terms of unanticipated nature, frequency, or severity) and are thought to represent an increased risk of harm to study participants
2) events which are not AEs but which add risk to participants or others (e.g. breach of confidentiality) should be reported on an expedited basis.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

- **Seriousness** of the AE:
  An AE is to be classified as "serious" (SAE) if it meets any of the following criteria:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.

Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/ Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (*e.g.,* sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (*i.e.,* death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An AE that meets none of the above criteria is considered "non-serious".

NOTE: Seriousness is independent of attribution or expectedness of the AE.

- **Expectedness** of the AE: In addition to term, grade, attribution, and seriousness, adverse events that have the potential to qualify for expedited reporting are to be designated as "expected" or "unexpected". For the purposes of determining expectedness, all of the adverse events listed in Section 7.2 are to be considered expected.

7.1 Adverse Event Management

Toxicities will be assessed according to NCI's CTCAE version 4.0.

Metformin is primarily associated with gastrointestinal side effects and if patients are not able to tolerate therapy based on these side effects, they will undergo a dose reduction. Management guidelines are listed below in the dose modification section 7.2. Metformin is rarely associated with lactic acidosis, in which case the drug will be discontinued and patients will receive appropriate clinical management.

Adverse events and toxicities will be captured both by planned laboratory studies at pre-specified timepoints (see study calendar) as well as by patient reporting. Patient interviews will be conducted weekly and drug diaries reviewed weekly during the initiation phase, and then monthly during the maintenance phase of treatment.

7.2 Dose modification

Gastrointestinal toxicities

Grade 1	Continue to follow treatment plan in section 5.1.2.
Grade 2	Maintain study agent at current dose. If

	resolves to grade 1 or less within 7 days, may increase Metformin dose as applicable. If does not resolve to grade 1 or less within 7 days, decrease to last tolerated dose level. If patient is on 500mg daily, then discontinue study treatment.
Grade 3	Decrease study treatment to last tolerated dose level. If toxicity does not resolve to grade 2 or less within 7 days, discontinue study treatment. If toxicity resolves to grade 2 or less within 7 days, may continue at lower dose level. Do not increase dose further.
Grade 4	Discontinue study treatment.

Renal toxicities

Estimated creatinine clearance <60ml/min	Hold study drug until creatinine clearance >60ml/min and at steady state, then may resume at last tolerated dose level.
Estimated creatinine clearance <30ml/min	Discontinue study treatment.

Metabolic toxicities

Symptomatic hypoglycemia Grade 1	Hold study drug until symptoms resolve to <grade 1, then may resume at last tolerated dose level if symptoms resolve within 7 days.
Hypoglycemia ≥Grade 2	Discontinue study treatment.
Acidosis ≥Grade 2	Discontinue study treatment.
Electrolyte abnormalities ≥Grade 3	Provide supportive care, hold study treatment until <grade 1. May resume at last tolerated dose or discontinue per investigator discretion.

Hematologic toxicities

Grade 1 or 2	Continue to follow treatment plan in section 5.1.2.
Grade 3	Maintain study agent at current dose. Transfuse if clinically indicated.
Grade 4	If patients meet criteria for worsening of cytopenias requiring removal of patient from study as defined in Section 5.5, then discontinue study drug. Otherwise, maintain study agent at current dose and transfuse if clinically indicated.

Other non-hematologic toxicities considered to be related to Metformin

Grade 1	Continue to follow treatment plan in section 5.1.2.

Grade 2	Maintain study agent at current dose. If resolves to grade 1 or less within 7 days, may increase Metformin dose as applicable. If patient is on 500mg daily, then discontinue study drug.
Grade 3	Decrease study treatment to last tolerated dose level. If patient is on 500mg daily, then discontinue study drug. If toxicity does not resolve to grade 2 or less within 7 days, discontinue study treatment. If toxicity resolves to grade 2 or less within 7 days, may continue at lower dose level. Do not increase dose further.
Grade 4	Discontinue study treatment.

8 DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

8.1 Safety Monitoring

The medical monitor will review and monitor toxicity and accrual data from this study. The medical monitor will be a clinical specialist with experience in hematology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The medical monitor will review this protocol up to four times per year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention; any response information; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

8.2 Stopping Rules Data

The study will be monitored to ensure that treatment related serious adverse events do not exceed the anticipated rate based on previous clinical studies. The study will be paused to accrual for review by the medical monitor, and may be terminated early if there are any grade V toxicities considered to be probably or definitely related to Metformin. If there are ≥3/24 patients with non-hematologic non-GI grade IV events that are attributed to be at least possibly related to Metformin which are observed during any point in the study, the study may be paused for accrual for evaluation by the medical monitor. Management for grade IV toxicities will be provided with guidance regarding holding medication and monitoring for resolution of toxicities (Section 7.2).

9 STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

9.1.1 Design

This is a pilot study to assess the hematologic activity and safety of Metformin in the Fanconi Anemia patient population.

9.1.2 Endpoints

Primary endpoint:

The primary endpoint is the proportion of subjects with a hematologic response.

Secondary endpoints:

- Secondary hematologic endpoints will evaluate change from baseline in:
  - hemoglobin
  - red cell transfusion requirements
  - platelet count
  - absolute neutrophil count
  - marrow cellularity
  - methylcellulose colony forming assays
- Safety: the proportion of subjects with adverse events by grade.
- Tolerability: median number of dose interruptions, median number of discontinuations, and proportion of patients who are able to achieve maximum dose of Metformin.
- Pharmacokinetics: pharmacokinetic profile and exposure of Metformin

Exploratory endpoints:

Exploratory biomarkers will describe change from baseline in:

- aldehyde-mediated damage
- chromosomal breakage and radial formation in response to DEB/MMC exposure
- cell cycling in CD34+ hematopoietic stem/progenitor cells
- serum insulin, fasting glucose, and oral glucose tolerance
- micronuclei formation in buccal swab samples

9.2 Sample Size, Accrual Rate and Study Duration

The total sample size is anticipated to be 24 patients. It is anticipated that without additional treatment, only 5% of patients would achieve a hematologic response. We would be interested in Metformin as a treatment in this patient population if the hematologic response rate is 20% or higher. The trial will be single arm, one-stage trial. The treatment will be considered promising if at least 3/22 subjects have a hematologic response. The probability of observing at least 3/22 responders is at least 0.84 assuming the true response is >=20% and is <10% if the true response is <5%. It is anticipated that we will need 24 patients to accrue 22 evaluable patients. Evaluable patients are defined in section 4.2.

It is anticipated that an average of 1-2 patients will enroll each month on study and the study duration is anticipated to be approximately 2 years.

9.3 Interim Analysis

Given that this is a pilot study of 24 patients, no interim analysis is planned.

The study accrual may be suspended if there are ≥3/24 patients with non-hematologic non-GI grade IV events that are attributed to be at least possibly related to Metformin which are observed during any point in the study, The probability of observing 3 or more events among 24 subject is equal to 0.89 if the observed rate is 20% and 0.12 if the observed rate is 5%."

9.4 Patient demographic and baseline characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, FA subtype, prior therapy, and baseline hematologic values (hemoglobin, platelet count, absolute neutrophil count, transfusion requirements) will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number (n), mean, standard deviation, standard error, median, range) will be provided. For categorical variables, patient counts and percentages will be provided.

9.5 Analysis of Primary Endpoints

Hematologic response will be defined by the modified MDS IWG criteria[24] which are provided in section 6.

Among evaluable patients (as defined in Section 4.2), hematologic response rate will be estimated and will be reported along with 90% binomial confidence intervals. Estimated response rates for each individual hematologic lineage will also be reported for hemoglobin/transfusion requirements for RBCs, platelet count, and absolute neutrophil count will also be reported along with 90% binomial confidence intervals. The time to hematologic response and duration of hematologic response will be reported for responders.

9.6 Analysis of Secondary Efficacy Endpoints

Changes in marrow cellularity pre and post treatment will be determined by a hematopathologist categorically (improvement in marrow cellularity or no improvement) and will be reported as a point estimate with 90% binomial confidence intervals.

Changes in methylcellulose colony forming assays pre and post treatment will be assessed. Mean changes will be estimated with Student's paired t-test for null hypothesis with binomial confidence intervals.

9.7 Analysis of Safety and Tolerability

Any patient that received at least one dose of drug would be eligible for the safety set. The proportion of patients with each toxicity overall and by grade will be reported along with 90%

confidence interval. This will be reported for the toxicities that are at least possibly related and regardless of attribution. The proportion of patients who required at least one dose reduction, who required at least one dose delay, who completed therapy and achieved the goal dose (diabetes/obesity-related dosing) of Metformin will be reported along with the 90% exact binomial confidence interval. The median number of dose reductions and dose delays will also be reported.

9.8 Analysis of Exploratory Endpoints

Change in exploratory endpoints before and after treatment will be compared using a paired t-test for aldehyde-mediated damage, chromosomal breakage, and radial formation in response to DEB/MMC exposure, micronuclei formation in buccal swab samples, percentage of cells in quiescence for cell cycling in CD34+ hematopoietic stem/progenitor cells, serum insulin, fasting glucose, and oral glucose tolerance test.

10 PUBLICATION PLAN

The results are expected to be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported. The initial release may be an abstract to be presented at a relevant scientific meeting. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

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APPENDIX A PERFORMANCE STATUS SCALES/SCORES

Performance Status Criteria
Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

Boston Children's Hospital

RESEARCH CONSENT FORM

This section only to be edited by IRB office.

Use Plate or Print:

MRN#:

DOB:

Subject's Name:

Gender:

Protocol Title: Pilot Study of Metformin for Patients with Fanconi Anemia

Principal Investigator: Elissa Furutani, MD

Co-Investigators: David Williams, MD, Akiko Shimamura, MD PhD and Erica Esrick, MD

Please check one of the following:

_____ You are an adult participant in this study.

_____ You are the parent or guardian granting permission for a child in this study.

If the participant is a child, the use of "you" refers to "your child."

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Participation in this research study is voluntary. You are free to say yes or no, and your decision will not impact the care you receive at Boston Children's Hospital (BCH). You can withdraw from the study at any time. A description of the study and its risks, its potential benefits, and other important information are in this consent form. Please read this consent form carefully and take your time making a decision. The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

How are individuals selected for this research study?

You are being invited to participate in this research study because you have Fanconi Anemia and have not yet had an allogeneic hematopoietic stem cell transplantation.

Why is this research study being conducted?

Fanconi Anemia (FA) is an inherited bone marrow failure disorder characterized by a DNA repair defect. FA patients have a high risk of developing bone marrow failure and certain types of cancer. Some patients have congenital anomalies including renal abnormalities, skeletal dysplasias, and skin abnormalities. Allogeneic hematopoietic stem cell transplantation can cure bone marrow failure; however, there are risks associated with stem cell transplant, and some patients may not be candidates for a stem cell transplant.

For patients unable or unwilling to undergo a hematopoietic stem cell transplant, some medications such as oxymethalone or danazol can improve blood counts in many patients with FA, though not all patients will respond, and some will lose their response over time. Patients on these medications remain at risk for leukemia or other serious side effects.

In this study, we want to learn whether a medication called Metformin is safe and tolerable for people with Fanconi Anemia. We also want to find out if taking Metformin helps improve blood counts in people with Fanconi Anemia.

Metformin is a medication taken by mouth (a pill) once or twice a day. Metformin is approved by the Food and Drug Administration (FDA) for glycemic control in adults and children as young as 10 years old with type 2 diabetes. In this study, the use of Metformin is investigational. This means the drug has not yet been approved by the FDA for the purpose we are studying: the treatment of Fanconi Anemia.

Who is conducting this research study, and where is it being conducted?

This single-site study is being done at Boston Children's Hospital (BCH). A grant from the Fanconi Anemia Research Foundation will provide funding for this study. Dr. Elissa Furutani is the principal investigator of this study.

Your health care provider may be a research investigator for this research and, as an investigator, is interested in both your clinical welfare and in the conduct of this study. Before entering this study or at any time during the research, you may ask for a second opinion about your care from another health care provider who is in no way associated with this project. You are not under any obligation to participate in any research project offered by your health care provider. If you choose not to participate or not to allow your child to participate, your care at BCH and/or with your health care provider will not be affected in any way at all.

How many people will participate in this research study?

Approximately 22-24 people will take part in this study at BCH.

What do I have to do if I am in this research study?

As a participant in this study, you will be provided Metformin, come to Boston Children's Hospital 2-3 times, go to a lab for a blood draw 5-7 times, have 8-9 phone calls with a research nurse, and you may take part in one pharmacokinetic assessment. Your participation will last about seven months: 6 months of receiving Metformin and then one follow-up phone call and blood draw approximately one month after discontinuing the medication. Below are descriptions of what will happen at each study visit. There is a schedule of visits after the descriptions.

Visit 1 – Baseline/Screening (BCH Visit)

At this visit, you will first be asked to review this consent form with the study doctor.

The Study Doctor will ask about your health and medical history and conduct a physical examination. This includes an overall assessment of your health and the measurement of height, weight, blood pressure, heart rate, breathing rate, and temperature.

You will be asked to produce a urine sample (about 5-10 mL or 1-2 teaspoons) to check for any blood cells, glucose (sugar), proteins, or chemicals, as well as for biomarker analyses.

You will be asked to brush the inside of your cheek with a toothbrush to collect cells. These cells will be used to look for changes in how your cells look. Once this testing has been completed, the cells will be discarded.

You will be asked to give a blood sample for standard laboratory testing. Around 17.5 mL (3.5 teaspoons) will be collected to check the following: levels of substances in the blood like chemicals, glucose, lipids (fats), minerals (like magnesium and calcium), iron, and any abnormal proteins; kidney and liver function; and blood-clotting ability.

You will be asked to have a pregnancy test performed, if applicable.

You will have a bone marrow. There are two parts to this test: an aspirate of liquid and a biopsy of solid bone marrow. The test involves putting a needle into the marrow space of your hip bone and removing a small amount of bone marrow. Before the test, you will be given a shot to numb the area and reduce the pain, or in some cases, you will be given sedation so that you are asleep. A sample of the liquid bone marrow (about 4 mL or 1 teaspoon) will be removed with the syringe. This amount of bone marrow may be safely removed.

Visit 2 (Start of Study Drug)
This visit will take place no more than 1 month after your baseline/screening visit and will involve the initiation of the study drug. If you do not live locally and cannot pick up the study drug from BCH, the study drug will be shipped to you. When you receive the study drug and take it for the first time, that day will be considered Day 1 of the study.

Visits 3-5 (Phone Calls)
A research nurse will call you each week. The nurse will ask you how you are feeling, if you have had any side effects from taking Metformin, and check if you are filling out your drug diary.

Visit 6 (Phone Call and Blood Draw or BCH Visit)
This visit will take place 1 month after you have started Metformin. You only need to have a blood draw. Around 3 mL (0.5 teaspoons) will be collected to check the following: levels of substances in the blood like chemicals, glucose, lipids (fats), minerals (like magnesium and calcium), iron, and any abnormal proteins; kidney and liver function; and blood-clotting ability. You can come to BCH to have this blood drawn, or you

can go to a lab that is more convenient to you if you do not live near BCH. If you want to have this blood drawn at a lab closer to you, the study team will discuss with you how to bring a request form to the lab and how the lab can send the report to BCH.

If you are able to come to BCH to for this visit, we would also like to have you give additional blood samples for pharmacokinetic testing. Pharmacokinetic testing looks at how your body processes the medication. This means that you would have a blood draw, take a dose of Metformin, and then have blood draws 1, 2, 4, and 6 hours after the dose. This means you would give another 7.5mL (1.5 teaspoons) of blood.

_____ (initials) I agree to participate in this optional pharmacokinetic testing.

A research nurse will also call you this week if you do not come to BCH. The nurse will ask you how you are feeling, if you have had any side effects from taking Metformin, and check if you are filling out your drug diary.

Visit 7 (Phone Call and Blood Draw)
A research nurse will call you a month later. The nurse will ask you how you are feeling, if you have had any side effects from taking Metformin, and check if you are filling out your drug diary.

You will also be asked to have a blood draw of 2 mL (0.5 teaspoons). You can come to BCH to have this blood drawn, or you can go to a lab that is more convenient to you if you do not live near BCH.

Visit 8 (Phone Call and Blood Draw)
This visit will take place 3 months after you have started Metformin. You will be asked to have a blood draw of 2 mL (0.5 teaspoons). You can come to BCH to have this blood drawn, or you can go to a lab that is more convenient to you if you do not live near BCH.

You will be asked to produce a urine sample (about 5-10 mL or 1-2 teaspoons) to check for any blood cells, glucose (sugar), proteins, or chemicals, as well as for biomarker analyses.

You will be asked to have a pregnancy test performed, if applicable.

A research nurse will also call you this week. The nurse will ask you how you are feeling, if you have had any side effects from taking Metformin, and check if you are filling out your drug diary.

Visits 9 and 10 (Phone Calls and Blood Draws)
A research nurse will call you once a month. The nurse will ask you how you are feeling, if you have had any side effects from taking Metformin, and check if you are filling out your drug diary.

You will also be asked to have a blood draw each month of 2 mL (0.5 teaspoons). You can come to BCH to have these blood draws, or you can go to a lab that is more convenient to you if you do not live near BCH.

Visit 11 – End of Treatment (BCH Visit)
This visit will take place 6 months after you have started Metformin. This is the last study visit, and you will stop taking Metformin.

The Study Doctor will conduct a physical examination. This includes an overall assessment of your health and the measurement of height, weight, blood pressure, heart rate, breathing rate, and temperature.

You will be asked to produce a urine sample (about 5-10 mL or 1-2 teaspoons) to check for any blood cells, glucose (sugar), proteins, or chemicals, as well as for biomarker analyses.

You will be asked to brush the inside of your cheek with a toothbrush to collect cells. These cells will be used to look for changes in how your cells look. Once this testing has been completed, the buccal swabs will be discarded.

You will be asked to give a blood sample for standard laboratory testing. Around 17.5 mL (3.5 teaspoons) will be collected to check the following: levels of substances in the blood like chemicals, glucose, lipids (fats), minerals (like magnesium and calcium), iron, and any abnormal proteins; kidney and liver function; and blood-clotting ability

You will be asked to have a pregnancy test performed, if applicable.

You will have a bone marrow test. There are two parts to this test: an aspirate of liquid and a biopsy of solid bone marrow. The test involves putting a needle into the marrow space of your hip bone and removing a small amount of bone marrow. Before the test, you will be given a shot to numb the area and reduce the pain, or in some cases, you will be given sedation so that you are asleep. A sample of the liquid bone marrow (about 4 mL or 1 teaspoon) will be removed with the syringe. This amount of bone marrow may be safely removed.

Visit 12 (Phone Call)

A research nurse will call you one month after you stop taking Metformin. The nurse will ask you how you are feeling, and if you still have any side effects from taking Metformin.

You will be asked to have a final blood draw of 2mL (0.5 teaspoons).

Schedule of Study Visits/Phone Calls

Study Visit Timeline	Visit 1 Screening	Visit 2	Visits 3-5 Phone Call	Visit 6 1 month	Visit 7 Phone Call	Visit 8 3 Month	Visits 9-10 Phone Call	Visit 11 6 month	Visit 12 Phone Call
		Day 1	Weekly	Month 1	Month 2	Month 3	Months 4 & 5	Month 6	Month 7
Consent/Assent	X								
Medical History	X								
Physical Exam	X							X	
Blood Draw	X			X	X	X	X	X	X
Urine collection	X					X		X	
Cheek Swab	X							X	
Bone Marrow	X							X	
Medication Diary		X	X	X	X	X	X	X	X
Phone call with research nurse			X	X	X	X	X		X

*Blood draw only if your baseline/screening visit occurred more than two weeks prior to you taking the study drug for the first time

What are the risks of this research study? What could go wrong?

Some procedures or treatments used in this research may present risks that are not well-known or understood. Therefore, there may be unforeseeable risks associated with participating in this research.

Risks of the study drug: Metformin

Here is a chart that explains most of the side effects of Metformin.

Possible Risk/Side Effect	How often has it occurred?	How serious is it?	Can it be corrected?
Diarrhea	About 50% of patients experience this	Not serious	yes
Nausea/vomiting	About 25% of patients experience this	Not serious	yes
Flatulence	About 12% of patients experience this	Not serious	yes
Asthenia (low energy)	Less than 10% of patients experience this	Not serious	yes
Indigestion	Less than 10% of patients experience this	Not serious	yes
Abdominal Discomfort	Less than 10% of patients experience this	Not serious	yes

Headache	Less than 10% of patients experience this	Not serious	yes

A very rare, but very serious, risk of taking metformin is lactic acidosis, meaning acid builds up in the blood. Call a doctor right away if you have any of the following symptoms, which could be signs of lactic acidosis:

- Feeling cold in your hands or feet
- Feel dizzy or lightheaded
- Slow or irregular heartbeat
- Feel very week or tired
- Unusual (not normal) muscle pain
- Trouble breathing
- Sleepy or drowsy
- Fever

Lactic acidosis is most likely to happen when you are not eating. If you have to have a test (like a CT) or a fasting blood draw, or if you have a stomach bug, you should contact the study team and hold the doses of Metformin until you are able to resume eating normally. You should hold doses of Metformin 24 hours before and after any imaging requiring contrast.

The drug to be used in this research study will not be given to you in a child resistant package. It must be stored out of the reach of children.

I understand that the drug is not in a child resistant package and understand that I must make sure that it is stored safely and out of the reach of children. _____ (initials of /parent/guardian)

Risks associated with bone marrow biopsy

At least one of the bone marrow assessments performed during your participation in this study is standard of care, so it would be performed regardless of participation in the study. The Study Doctor will inform you in detail about the risks associated with this procedure. In general, having an aspirate/biopsy can cause pain, swelling, bleeding and/or infection at the site where the needle penetrates through the skin. The likely risks and side effects of having a biopsy include:

- Minor local bleeding or pain at the needle site, a swelling under the skin that contains blood, and sleepiness if the Study Doctor recommends a "pain killer" and/or medicine to help you relax.

Unlikely but serious risks and side effects from having a biopsy include:

- Infection, serious bleeding, and, if the Study Doctor recommends a "pain killer" and/or medicine to help you relax, the following may occur: shortness of breath, slow heart rate, and low blood pressure.
- You may be given sedation to make you sleep during this bone marrow biopsy. This sedation is optional, and you will sign a separate anesthesia consent form. That consent form will describe the risks of sedation in depth, but briefly, they are: shortness of breath, slow heart rate, and low blood pressure. You will be monitored for these risks during the biopsy.

Risks of an Oral Glucose Tolerance Test (OGTT)

You will be required to fast for approximately 10 hours before your OGTT. This may make you feel hungry and lightheaded. We will try to get these tests done in the morning and then provide breakfast. The glucose solution you will need to drink may taste bad.

Risks of blood draw
Risks associated with a blood draw may include minor discomfort, bruising, fainting, and infection. When possible, we will draw blood at the time of a clinically-indicated procedure to reduce the number of needle sticks.

Risks of cheek swab
Risks associated with a check swab may include minor discomfort and unpleasant taste.

Reproductive Risks
The effects of the drug being studied on the reproductive system (sperm, eggs) or to the developing fetus are unknown. For this reason, female participants taking the drug should not become pregnant. All participants must agree not to have sexual intercourse or to use a reliable, effective birth control during the study. If you have a female partner who is able to become pregnant, one or both of you must use some form of effective birth control. During the research, if your partner becomes pregnant, or if there is a chance that she is pregnant, you should contact the research investigator immediately so that we may provide medical assistance and counseling.

Pregnancy testing will be performed before the research begins. The results of the pregnancy test are confidential and will be given to your child by one of the study nurses or doctors in private. We would not tell parent(s) or guardian(s) without your permission. However, under certain circumstances, we might be compelled to reveal this information. For example, if your life was at risk or if abuse was suspected, it may be necessary to inform your parent(s) or guardian(s) or relevant authorities.

If we believe it's necessary to tell a parent or guardian about a positive pregnancy test, we would ask permission from you. However, if we feel it is necessary to tell a parent/guardian without your permission we would first meet with you in private to discuss our concerns before divulging any information regarding pregnancy. During research, if you have a positive pregnancy test, we must withdraw you from the research. This means that even if we do not reveal the results, parent(s) or guardian(s) may suspect that their child is pregnant despite our best efforts to maintain confidentiality. If you become pregnant or if there is any chance that you are pregnant (late menstrual period), please contact the research investigator immediately so that we may provide medical assistance and counseling.

What are the benefits of this research?

We do not know if participating in this study will benefit you. We hope to learn more about whether Metformin can help improve blood counts. The bone marrow assessments that you will have during this study will provide information about how you may or may not be responding to Metformin treatment and also provide information on possible disease progression.

Are there costs associated with this research? Will I receive any payments?

Metformin will be provided to you at no cost. You will receive a parking voucher for each study visit at Boston Children's Hospital. Other reasonable travel expenses can be reimbursed with prior approval from the research team. More information about this reimbursement process can be found in the Metformin Study Participant Reimbursement Guide.

This research study will use a service called ClinCard® by the company Greenphire, www.greenphire.com, to manage all payments associated with your participation in study visits, your time, and travel related to participation in the study. ClinCard/Greenphire will provide documentation for filing your taxes (1099 form), to the hospital, and may ask for your name and social security number using a secure website to meet that federal requirement. Boston Children's Hospital or the sponsor has contracted with ClinCard/Greenphire to provide this service, but Boston Children's Hospital and ClinCard/Greenphire are separate entities and have no other relationship. ClinCard/Greenphire is solely responsible for the security of any information you provide to them.

You will be issued a ClinCard, which is a specially designed debit card for clinical research onto which your funds will be loaded as appropriate. When a study visit is completed, funds will be loaded onto your card. The funds will be available within 1 day and can be used as you wish.

Research funds will pay for both of the bone marrow procedures that you will have at Boston Children's Hospital. When you have the monthly lab tests done at your local lab, this lab may bill your health insurer for routine items and services you would have received even if you did not take part in this research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the research staff.

We will offer you the care needed to treat any injury that directly results from taking part in this research. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form. If you think you have been injured or have experienced a medical problem as a result of taking part in this research, tell the person in charge of the research as soon as possible. The researcher's name and phone number are listed in this consent form.

If you go to the Emergency Room or to another hospital or doctor, it is important that you tell them that you are in this research. If possible, you should give them a copy of this consent form.

If I do not want to take part in this research, what are the other choices?

If you do not join this research your doctor can discuss other healthcare choices with you. Your other choices may include:

- Androgens such as oxymetholone or danazol
- Allogeneic hematopoietic stem cell transplantation
- Receiving Metformin off-label, meaning without participating in a research study
- Joining a different research study

Are there other things I should know about?

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research, we will let you know as soon as possible.

Some of your blood and bone marrow samples will be sent to the Dana Farber Cancer Institute Fanconi Anemia Center, University of North Carolina, and Fred Hutchinson Cancer Research Center. These institutions will perform some of the research tests for this study. Your samples will be sent with a code, so these other institutions will not be able to identify you.

Why would I be taken off the study early?

The research investigator may take you out of this study at any time. This would happen if:

- The research is stopped.
- You are not able to attend the research visits required.
- You fail to follow the research requirements.
- You need a treatment or medication that may not be taken while on the research or the research investigator feels it is in your best interest to be taken out of this research.

If this happens, the research investigator will tell you.

Other information that may help you:

Boston Children's Hospital has developed a web-based, interactive educational program for parents called "A Parent's Guide to Medical Research." To find out more about research at Children's, please visit the program at www.researchchildren.org.

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between the hours of 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will be placed in your medical record. If you do not have a medical record at Boston Children's Hospital, one will be created for you.

Information collected during this research will become part of your medical record if the information is related to the care you receive at Boston Children's Hospital. Medical records are considered permanent records; therefore, information cannot be deleted from the record. Medical records are available to health care professionals at Boston Children's Hospital and may be reviewed by Hospital staff when carrying out their responsibilities; however, they are required to maintain confidentiality in accordance with applicable laws and Hospital policies. Information contained in your medical record may not be given to anyone unaffiliated with Boston Children's Hospital in a way that could identify you without written consent, except as required or permitted by law.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. law. This web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this web site at any time.

Contact for Future Studies: Your participation in any research is completely voluntary, and you should feel no pressure to participate if you are contacted about another research study.

Please check and initial one of the options below regarding future contact about other research done by us or other researchers we are working with (collaborators).

_____ ☐ Yes, I may be contacted about participating in other research projects studying Fanconi Anemia or related conditions. I give permission for my contact information (name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;

- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;
- People at Boston Children's Hospital who oversee, advise, and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Companies that manufacture drugs or devices used in this research;
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston Children's Hospital, including services providers, such as laboratories and others;
- And/or your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling.

Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done.

We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes. However, your name or identifying information will not be used without your specific permission.

Your privacy rights

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future, and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however you cannot get back information that was already shared with others. Once you remove your permission, no more private health

information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment, or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Contact Information

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At…	If I have questions or concerns about…
Principal Investigator: **Elissa Furutani, MD**	Phone: **617-355-8246** Pager: 617-355-6363 **Pager #4847**	▪ General questions about the research ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Study Coordinator **Ashley Galvin**	Phone: **857-218-3736**	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Institutional Review Board	Phone: **617-355-7052**	▪ Rights of a research participant ▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.

Documentation of Informed Consent and Authorization

- I have read this consent form and was given enough time to consider the decision to participate in this research.
- This research has been satisfactorily explained to me, including possible risks and benefits.
- All my questions were satisfactorily answered.
- I understand that participation in this research is voluntary and that I can withdraw at any time.
- I am signing this consent form prior to participation in any research activities.
- I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■_____ _____ _____

Date (MM/DD/YEAR) Signature of **Parent #1** or **Legal Guardian** Relationship to child

Child Assent

■_____ _____

Date (MM/DD/YEAR) Signature of **Child/Adolescent Participant**

■ If child/adolescent's assent is **not** documented above, please indicate reason below (check one):

☐ Assent is documented on a separate IRB-approved assent form
☐ Child is too young
☐ Other reason (e.g. sedated), please specify: _____

Adult Participant (if applicable)

■_____ _____

Date (MM/DD/YEAR) Signature of **Adult Participant (***18+ years)*

Research Investigator /or Associate's Statement & Signature

- I have fully explained the research escribed above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).
- I have answered and will answer all questions to the best of my ability.
- I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and benefits during or after the course of the research.
- I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■_____ _____

Date (MM/DD/YEAR) Signature of **Research Investigator or Associate**

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative, **or**

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent **or**

☐ Situations where the IRB requests a witness be present: please specify _____

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

Or

☐ The individual is not English speaking and, through an interpreter, a short form consent document was presented orally to the participant or legal representative and this consent document serves as the summary for such consent.

I confirm that the information in this consent form was presented orally to the participant, parent or legally authorized representative, in a language they could understand and the individual had the opportunity to ask questions.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness