OPT-JIA Statistical Analysis Plan

TRIAL FULL TITLE	**The Ondansetron Premedication Trial in Juvenile Idiopathic Arthritis, OPT-JIA**
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TRIAL STATISTICIAN	Dr. Thomas Loughin
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TRIAL PRINCIPAL INVESTIGATOR	Dr. Jaime Guzman
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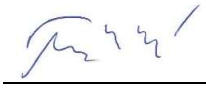
1 SAP Signatures

I give my approval for the attached SAP entitled **The Ondansetron Premedication Trial in Juvenile Idiopathic Arthritis, OPT-JIA,** dated January 30th, 2024.

Statistician
Name: Dr. Thomas Loughin

Signature: 

Date: 2024-01-30

Principal Investigator
Name: Dr. Jaime Guzman

Signature: 

Date: 30 Jan 2024

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3 Abbreviations and Definitions

AE	Adverse Event
CAPRI	Canadian Alliance of Pediatric Rheumatology Investigators
CRF	Case Report Form
CRP	C-Reactive Protein
DMARD	Disease-Modifying Antirheumatic Drug
DSC	Data and Safety Committee
ESR	Erythrocyte Sedimentation Rate
EQ-5D-Y	EuroQol group 5-dimension quality of life questionnaire for youth
ILAR	International League of Associations for Rheumatology
IMP	Investigational Medical Product
JIA	Juvenile Idiopathic Arthritis
MISS	Methotrexate Intolerance Severity Score
n	number
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OPT-JIA	Ondansetron Premedication Trial in Juvenile Idiopathic Arthritis
PGA	Physician Global Assessment
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SUSAR	Suspected Unexpected Serious Adverse Reaction

4 Introduction

4.1 Preface

Methotrexate is the most widely used disease-modifying anti-rheumatic drug (DMARD) for the treatment of children with Juvenile Idiopathic Arthritis (JIA). In children, methotrexate side effects such as nausea, vomiting and abdominal discomfort can lead to conditioned methotrexate intolerance with anticipatory nausea/vomiting and avoidance behaviours (in up to 50% of children). Methotrexate intolerance leads to poor adherence to optimal dosing or to stopping the medication altogether. Children who cannot adhere to optimal dosing or stop methotrexate may require expensive biologic medications to control their JIA.

The Ondansetron Premedication Trial in Juvenile Idiopathic Arthritis (OPT-JIA) is a registry-based pragmatic adaptive superiority randomized clinical trial to evaluate if routine premedication with the anti-emetic ondansetron reduces methotrexate intolerance and increases the proportion of children with JIA able to continue taking methotrexate, resulting in a better quality of life and more cost-effective medication use. OPT-JIA is a Health Canada regulated trial that adheres to the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for design, analysis and reporting.

All OPT-JIA data is collected via the Canadian Alliance of Pediatric Rheumatology Investigators (CAPRI) JIA Registry. The CAPRI Registry captures information on clinical characteristics, outcomes and adverse events of children with JIA across all Canadian pediatric rheumatology centres, at every visit to clinic. The Registry started in 2017, and as of October 2023, it contains information on >1200 children. OPT-JIA does not have fixed time intervals for data collection. Data is collected for one year after study enrolment at clinic visits that are scheduled according to patient needs.

4.2 Scope of the analyses

The OPT-JIA protocol contemplates three main analyses: safety analyses every 6 months, one interim efficacy analysis and a final analysis of safety and efficacy. The 6-monthly safety analysis is descriptive and consists of a Table summarizing the characteristics of enrolled subjects and a Table listing reported adverse events.

This Statistical Analysis Plan describes the details of the interim (preliminary) efficacy analysis and the final analysis of safety and efficacy. It specifies the changes made relative to the analysis plan outlined in the OPT-JIA protocol V3, approved by Health Canada in September 2020.

5 Study Objectives and Endpoints

5.1 Study Objectives

(ICH E3; 8.)

The aim of OPT-JIA is to determine the effectiveness of prophylactic use of ondansetron in patients with JIA starting methotrexate in Canadian pediatric rheumatology practices (intervention), compared to as-needed use in those children who develop nausea/vomiting (control).

Specific Objectives:
To compare:
1) The proportions of patients remaining on methotrexate with no intolerance between the two groups one year after starting methotrexate (primary endpoint).
2) The safety and tolerability of premedication with ondansetron, compared to as needed use.
3) The 1-year cumulative incidence of: a) methotrexate intolerance, b) attainment of inactive disease, c) biologic medication initiation
4) The mean quality of life scores and methotrexate intolerance severity scores between the two groups 4-8 months after starting methotrexate.

OPT-JIA also collects information on impacts on quality of life (to calculate health utilities) and medication utilization that will enable a future cost-effectiveness analysis.

5.2 Endpoints

(ICH E9; 2.2.2)
Primary endpoint:
Proportion of subjects that remain on methotrexate with no intolerance one year after starting methotrexate. Intolerance is defined as ≥6 points in the English or French versions of the validated Methotrexate Intolerance Severity Score, MISS [1, 2]. The MISS questionnaire can be found in the appendix.

Secondary endpoints:
1) frequency and cumulative incidence of adverse events and any serious unexpected suspected adverse drug reactions (SUSARs).
2) the cumulative incidence of methotrexate intolerance within one year;
3) the cumulative incidence of attainment of inactive disease within one year defined by Wallace criteria [3] as modified by Guzman et al [4];
4) the cumulative incidence of starting a biologic medication within one year; and
5) the mean quality of life scores in the Quality of My Life scale 4-8 months after starting methotrexate [5];
6) the mean scores in the MISS questionnaire 4-8 months after starting methotrexate.

To enable future cost-effectiveness analysis, the EuroQol Collaboration 5-dimension scale for quality of life for youth parent-proxy questionnaire (EQ-5D-Y) is completed at every visit, for calculation of quality-adjusted life years [6], and medication costs will be calculated using the prices from the Ontario Drug Benefit Formulary [7].

Assessment of outcomes are completed at all clinic visits scheduled as per medical need using the CAPRI Registry (usual practice is every 1-4 months). OPT-JIA does not include additional trial-specific visits.

6 Study Methods

6.1 General Study Design and Plan

(ICH E3;9) (ICH E3; 9.2, 9.7.1, 11.4.2.7. ICH E9; 3.3.2)

Children (ages 4-16 years) in the CAPRI JIA Registry who are starting methotrexate for the first time are eligible to participate in OPT-JIA. The target sample is 176 children followed for one year after starting methotrexate. Patients are followed every 1-4 months as clinically indicated. Outcomes are assessed via online data collection into the Registry at all clinic visits. The OPT-JIA protocol calls for an interim efficacy analysis completed after 90 children are recruited. The analysis results are to be used by an independent data and safety committee (DSC) to review for any needed adjustments to the target sample size, or study termination for success or futility.

OPT-JIA is a CAPRI JIA Registry-based pragmatic adaptive superiority RCT. OPT-JIA trial schema is reproduced in Figure 1 below.

Registry-based: The trial uses infrastructure already in place for the CAPRI JIA Registry [8].

Pragmatic: Broad inclusion criteria and simple outcome assessments compatible with usual care.

Adaptive: OPT-JIA is a Planned Sample-Size Re-Estimation Adaptive Trial as described by Bhatt & Metha [9].

Superiority: Designed to test superiority (as opposed to non-inferiority) of ondansetron premedication.

RCT: Treatments assigned by block randomization and analyses adjusted for post-randomization imbalances. Patients are randomized online via the REDCap [10] Registry plug-in using a 1:1 block randomization by Canadian region of residence and patient weight (<15Kg, 15-30Kg, >30Kg) with randomly assigned block size to ensure allocation concealment [11]. There is no blinding.

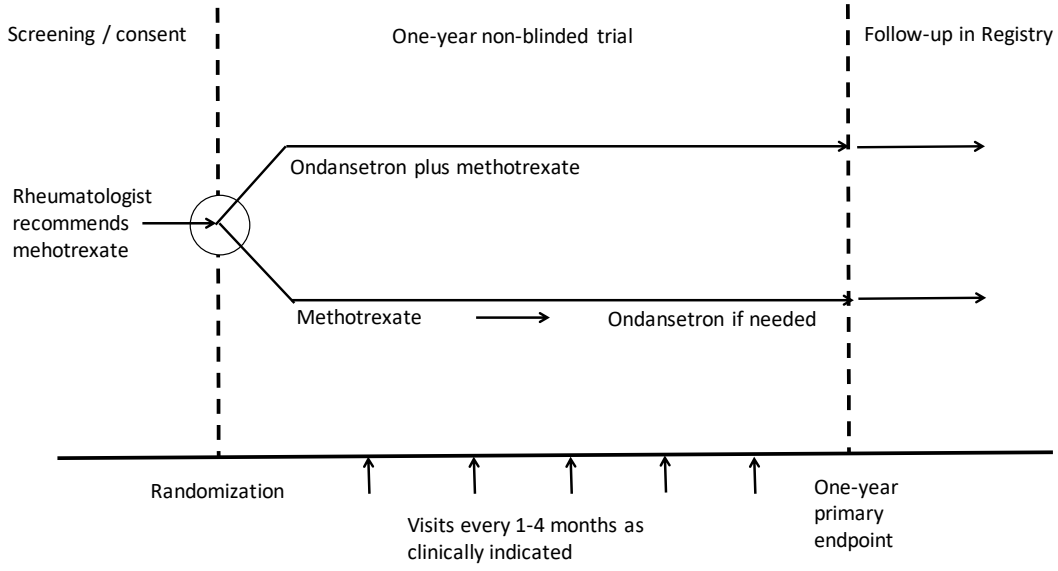

Figure 1: Trial schema for the Ondansetron Premedication Trial in Juvenile Idiopathic Arthritis (OPT-JIA).

Children in the intervention group are prescribed premedication with oral ondansetron (2 mg if <15Kg, 4 mg if 15-30Kg, 8 mg if >30Kg) to be taken one hour before each weekly methotrexate dose, followed by two additional doses every 6-8 hours if awake. All children receive methotrexate and folic/folinic acid as per the rheumatologist's usual practice. Current North American guidelines recommend a dose of methotrexate of 10-20 mg/m2 weekly subcutaneously or orally to a maximum of 25mg/week, at the discretion of physician and family [12, 13]. Folic/folinic acid is commonly used as 1mg orally daily or 5-10mg orally weekly.

Children in the control group receive methotrexate and folic/folinic acid as per the physician's usual practice. Those who report nausea/vomiting during regular care are prescribed ondansetron at the same dose and schedule as above, as per the attending rheumatologist's discretion. This is the current practice at BC Children's Hospital and other Canadian centres.

Ondansetron is offered in three forms: tablets (4mg, 8mg), oral solution (4mg/5ml) and oral disintegrating tablets (4mg, 8mg). Tablets can be swallowed or crushed and mixed with food. Ondansetron will be prescribed as tablets, unless the physician and family decide to use liquid or oral disintegrating tablets instead. The dose will be the same.

6.2 Inclusion-Exclusion Criteria and General Study Population

(ICH E3;9.3. ICH E9;2.2.1)

Subject inclusion criteria:

1. Ages 4-16 years
2. Diagnosis of JIA as per International League of Associations for Rheumatology ILAR criteria [14]
3. Followed at a CAPRI centre in Canada
4. Starting methotrexate to control JIA manifestations (arthritis, uveitis, psoriasis). (Female subjects of child bearing potential who are taking methotrexate for JIA cannot be pregnant, breastfeeding, or planning a pregnancy while on the drug and females of childbearing potential who are sexually active must use highly effective medically acceptable contraception. Subjects who stop methotrexate during the study will also discontinue ondansetron.)
5. Informed written consent to participate
6. Participating in the CAPRI JIA Registry

Subject exclusion criteria:

1. Previous use of methotrexate
2. Known hypersensitivity to ondansetron or any components of its formulations
3. Known hypersensitivity to other 5-HT3 antagonists
4. Known congenital Long-QT syndrome
5. Patients taking other medicinal products that lead to either QT prolongation or electrolyte abnormalities
6. Because the serotonin syndrome may occur when ondansetron is combined with other agents that may affect the serotonergic neurotransmitter system, patients receiving any of the serotonergic and/or neuroleptic drugs listed below will be excluded:
    - Triptans, SSRIs, SNRIs, lithium, sibutramine, fentanyl and its analogues, dextromethorphan, tramadol, tapendalol, meperidine, methadone, pentazocine or St. John's Wort (Hypericum perforatum), MAOIs, linezolid, methylene blue.
7. Patients who are pregnant or breastfeeding, or are sexually active and unwilling to practice an acceptable method of birth control.
8. Family unable to complete questionnaires in English or French

6.3 Randomization and Blinding

(ICH E3; 9.4.3, 9.4.6. ICH E9; 2.3.1, 2.3.2)
Patients are assigned 1:1 online after confirming eligibility, using the Registry and block randomization by Canadian region and patient weight to one of two groups:

Intervention	routine premedication with oral ondansetron (2 mg if <15Kg, 4 mg if 15-30Kg, 8 mg if >30Kg; 3 doses a week)
Control	oral ondansetron at the same dosing, prescribed only to those who develop methotrexate-induced nausea/vomiting during usual care.

There is no blinding (masking) of treatment assignment.

6.4 Study Assessments

(ICH E3; 9.5.1. ICH E9; 2.2.2)

Visit	Baseline	Every Visit	Visit Month 12
History and examination	x	x	x
QOL questionnaire	x	x (± 14)	x (± 14)
MISS	x	x (± 14)	x (± 14)
Actionable AEs	x	x	x
SAEs	x	x	x
SUSARs	x	x	x
Concomitant medication	x	x	x
Methotrexate use and dose	x	x	x
Ondansetron use and dose	x	x	x

Analysis Time Windows

Visit (target day)	*Lower bound (days)*	*Upper bound (days)*
Baseline (0)	*N/A*	*N/A*
Every visit to clinic (time window not applicable)	*N/A*	*N/A*
Month 4-8 (180)	*120*	*240*
Month 12 (364)	*308*	*420*

7 Sample Size

(ICH E3; 9.7.2. ICH E9; 3.5)
Our primary outcome statistic is the ratio of two proportions (relative risk, RR): the proportion of randomized children remaining on methotrexate with no intolerance in the intervention group divided by the same in the control group. Our sample size calculation is based on expressing the RR in the log scale and using established formulas for standard errors [15, 16]. With $p<0.05$, power of 90% and expected methotrexate continuation with no intolerance of 50% in the control group and 75% in the intervention group the result is 79 evaluable subjects per group. We will aim to recruit 176 subjects total to allow for up to a 10% dropout rate.

8 General Analysis Considerations

8.1 Timing of Analyses

The "6-monthly" safety analysis is completed before the meetings of the DSC and its precise timing depends on the dates booked for DSC meetings.

The interim analysis was planned at the time 90 subjects had been recruited in OPT-JIA but it was rescheduled with approval of the DSC and the Steering Committee, to occur on September 30th, 2023 due to slow recruitment, as explained in section 8.5 below.

The final analysis is to be conducted after the final sample size is achieved or at the time the study is stopped. All subjects enrolled in the study at that time will complete a one-year follow-up and will be included in the final analysis.

8.2 Analysis Populations

(ICH E3; 9.7.1, 11.4.2.5. ICH E9; 5.2)
The primary analysis will be conducted on the intention-to-treat population, including all randomized subjects. A secondary per-protocol analysis will be conducted on those subjects who received the assigned intervention for at least 3 months (ondansetron and methotrexate in the intervention group, methotrexate in the control group). Because it was clear at the time of interim analysis that some patients stopped methotrexate before 3 months due to intolerance, the per protocol analysis was modified to also include patients who stopped the medication before 3 months due to intolerance or toxicity.

8.3 Covariates and Subgroups

(ICH E3; 9.7.1, 11.4.2.1. ICH E9; 5.7)
The following covariates at baseline will be used to define if post-randomization imbalances have occurred: age, sex, months since JIA diagnosis, JIA category, active joint count, physician global assessment of disease activity, parent global assessment of wellbeing, c-reactive protein level, erythrocyte sedimentation rate, body weight strata, previous treatment and presence of uveitis.

If imbalances have occurred ($p<0.1$), the imbalanced variables will be used in logistic regression models to adjust efficacy estimates. OPT-JIA does not include any subgroup analyses.

8.4 Missing Data

(ICH E3; 9.7.1, 11.4.2.2. ICH E9;5.3. EMA Guideline on Missing Data in Confirmatory Clinical Trials)

During ongoing quality control of data entered in the study database, data from a study visit is reviewed by the study registry coordinator within 2 weeks of being entered and queries are sent to the site regarding any missing or apparently spurious data. Once these queries are answered satisfactorily, the data for that visit is locked. Only data contained in locked visits will be used for trial analyses.

In preparation for the interim and final analyses, the study statistician will perform further examination of the data for outlier values. Values outside a plausible range (e.g. an erythrocyte sedimentation rate >200 mm/h) will be converted to missing values.

After receiving the locked study dataset for the final analysis and dealing with values outside a plausible range, missing values will be imputed if needed using multiple imputations by chained equations.

Missing MISS questionnaire scores will not be imputed. Subjects with missing MISS questionnaire scores while still receiving methotrexate will be considered as censored as of the last available visit with a valid MISS score.

8.5 Interim Analyses and Data Monitoring

(ICH E3; 9.7.1, 11.4.2.3. ICH E9; 4.1, FDA Feb 2010 “Guidance for Industry Adaptive Design Clinical Trials for Drugs and Biologics”)

The OPT-JIA protocol (V3, September 2, 2020) called for a preliminary analysis to be used by an independent data and safety committee (DSC) to review for any needed adjustments to the target sample size, or early termination of the trial.

The interim analysis was to be conducted once 90 patients had been recruited to the trial. All follow-up information available at that point was to be used to calculate a two-sided 95% confidence interval (CI) for the relative risk of continuing on methotrexate with no intolerance, where the confidence level is adjusted for information accrual as per Schoenfeld [15].

8.5.1 Purpose of Interim Analyses

The purpose of the interim analysis is to obtain a preliminary assessment of efficacy to assess trial progress to date, deciding whether to continue the trial and/or re-estimate the sample size. Decisions arising from the interim analysis include continuing to the original planned sample size, changing the sample size respecting the evidence gathered to date, or terminating the trial. Termination could be either because of overwhelming evidence of superiority of the ondansetron intervention or because of statistical futility measured by overwhelming evidence that the intervention did not improve retention on methotrexate without intolerance.

8.5.2 Planned Schedule of Interim Analyses

The single interim analysis was originally planned after recruitment of 90 children. As explained in the scope of adaptation below, due to slower than expected recruitment this was changed in the spring of 2023 by the OPT-JIA Steering Committee in consultation with the Data and Safety

Committee to be conducted with patients recruited as of September 30th, 2023, irrespective of the number of subjects.

8.5.3 Scope of Adaptations

The trial steering committee, with approval from the DSC, elected to conduct the interim analysis at an earlier stage of the trial than initially planned. Because of challenges relating to the COVID19 pandemic and other reasons, recruitment into the study had been much slower than anticipated, and there were concerns that the initial planned sample size might be unattainable within a reasonable time frame. The interim analysis was rescheduled to take place using all available enrolments into the study as of September 30, 2023.

Because the analysis would be based on a much smaller fraction of the intended sample size, the OPT-JIA PI and the study statistician proposed, and the DSC agreed, to base the analysis on the confidence interval for relative risk computed using the ratio of two estimates of the probability of successful trial completion from independently estimated Kaplan Meier curves. These estimates would better account for the partial information available from patients who did not have sufficient time in the study to complete the 52-week observation period.

To make use of all available information from patients who had not completed the trial yet, the definition of the primary end point was modified as follows. Visit times were shown in weeks since enrolment in OPT-JIA. We used 52 weeks to represent the 1-year visit as required for determining success. Failure was determined to have occurred if any of the criteria for failure -- stopping methotrexate or experiencing intolerance -- were observed during any visit up to and including 52 weeks. Success was determined to have occurred if no failure criteria were met at or before 52 weeks, and the patient had at least one visit at or after 52 weeks. All other patients were considered censored as of the time of their last visit; i.e., they were known not to have failed yet, but they had not yet provided a visit at or beyond 52 weeks to declare success.

The second adaptation was the use of the O'Brien-Fleming adjustment to type 1 error rate for the calculation of the confidence interval in the interim analysis [17]. This adjustment resulted in calculation of a 99.55% confidence interval for the interim analysis instead of the 95% mentioned in the protocol. The rationale being that both the interim and the final analysis together would then have a 5% chance of a positive result if the intervention is no more effective than control.

8.5.4 Stopping Rules

As per the study protocol, the Data and Safety Committee assess results of the preliminary analysis according to the following guidance:

- If the CI is entirely below a relative risk of 1.2, the study will be stopped for futility.
- If the CI is entirely above a relative risk of 1.2, the study will be stopped and superiority will be claimed.
- If the CI includes a relative risk of 1.2, the trial will continue until the re-calculated full target sample is attained.

The RR of 1.2 was selected on clinical grounds. In a prospective study of 142 children with JIA starting methotrexate followed for one year, Van Dijkhuizen et al reported that 59 patients developed intolerance and 11 discontinued methotrexate for other reasons, for a total of 72 (50.7%) remaining on methotrexate with no intolerance [18]. An increase in this proportion to <60% is deemed too small to justify the additional costs and risks of adding prophylactic ondansetron.

8.5.5 Analysis Methods to Minimize Bias

Although OPT-JIA is not a blinded RCT, the two components of the primary endpoint are robust and unlikely to be influenced directly by the OPT-JIA investigators or the statisticians. Whether a patient is receiving methotrexate or not is a verifiable occurrence not under their control, and intolerance is defined directly by the parents by answering a validated questionnaire. Further, there is no pharmaceutical sponsor for OPT-JIA and the medications being tested have been marketed as generic medications in Canada for >20 years, making bias introduced by a pharmaceutical sponsor not possible.

8.5.6 Adjustment of Confidence Intervals and p-values

We use the O'Brien-Fleming adjustment to type 1 error rate for the interim analysis. This adjustment is based on the "alpha-spending" principle that guarantees that no conclusions from the trial have more than a 5% chance of a positive result if the intervention is no more effective than control. The adjustment uses a substantially reduced alpha level for the interim analysis, making it more difficult to terminate the trial prematurely due to chance outcomes. The final analysis of the primary outcome uses the remaining alpha not used (0.05 minus the amount used in the interim, 0.0045), and combines the data from both stages of the trial into one final test statistic.

8.5.7 Interim Analysis for Sample Size Adjustment

Upon completion of the interim analysis, a new sample size estimate is calculated using simulation techniques. Simulation answers the following question: given our current data, and assuming that our initial expectations for success probability in the two arms remain true (75% in intervention, 50% in control), how many more patients would need to be enrolled in order to maintain a 90% chance that the final analysis produces a 95% confidence interval for the relative risk that lies entirely above 1.2?

We use simulation techniques because the binary success/failure outcome is easy to simulate accurately from any expected probability specifications and for any size of patient sample. The simulation involves creating hypothetical future results using the expected success probabilities for a new set of *n* patients in each treatment group, adding the current results to these simulated future results, conducting the final analysis on the complete set of results, and observing whether the confidence interval lies entirely above 1.2. We perform this simulation and analysis process 10,000 times, and the proportion of these replicates in which the interval lies above 1.2 is an accurate estimate of the power for the study using *n* new patients per group. By repeating the process for a variety of values of *n*, we can identify the smallest sample size that achieves 90% power.

8.5.8 Practical Measures to Minimize Bias

The interim analysis is conducted by a PhD student in the Department of Statistics and Actuarial Science at Simon Fraser University, working under the direct supervision of the study statistician. Neither the statistician nor the student has a financial stake in the outcome of the trial. They receive only the data necessary to conduct the analysis and confirm its accuracy.

The results of the interim analysis are presented to the DSC by the study statistician and the DSC is charged with making a recommendation to the PI as to the advisability of continuing the trial.

OPT-JIA does not have a pharmaceutical sponsor and all medications tested in the trial are medications currently marketed in Canada and available as generic medications. The study PI, Dr. Jaime Guzman, serves as the trial sponsor in Health Canada submissions.

As per the OPT-JIA DSC Charter, Dr. Jaime Guzman will consider the recommendation of the DSC. If the recommendation is to continue the trial to attain the newly calculated sample size, Dr. Guzman will consider the feasibility of this approach given available study funding and the observed recruitment rate. No information will be made public until a final determination is made.

Because the intervention requires all parties in the trial to act differently from the control, there is no blinding in the trial, and hence no need for additional measures during the statistical analysis to preserve blinding.

8.5.9 Documentation of Interim Analyses

All interim analysis data files, preliminary statistical output and final interim analysis report for the DSC will be preserved in the OPT-JIA Trial folders at the institutional computer servers controlled by the BC Children's Hospital in Vancouver, under the custody of Dr. Jaime Guzman. Copies of all email communications pertaining the interim analysis between the study biostatisticians, study PI and the chair of the DSC will also be preserved in these folders.

9 Summary of Study Data

All variables will be summarized separately for subjects assigned to the intervention and to the control group and shown in side-by-side columns in tables in that order. Descriptive categorical variables at baseline will be summarized as frequencies and percentages. Descriptive continuous variables at baseline will be summarized as medians and 25^{th} and 75^{th} centiles. Efficacy categorical variables will be summarized as frequency and percentages. Efficacy continuous variables (MISS scores and quality of life scores) will be summarized as means and standard deviations.

Between-groups comparisons of baseline characteristics will be made using Fisher exact tests for categorical variables and the Wilcoxon rank sum test for continuous variables, and the corresponding p value reported. All tests will be double sided and p values <0.05 will be considered statistically significant.

9.1 Subject Disposition

Subject disposition will be reported as per the CONSORT statement [19] using the skeleton chart reproduced in Figure 2.

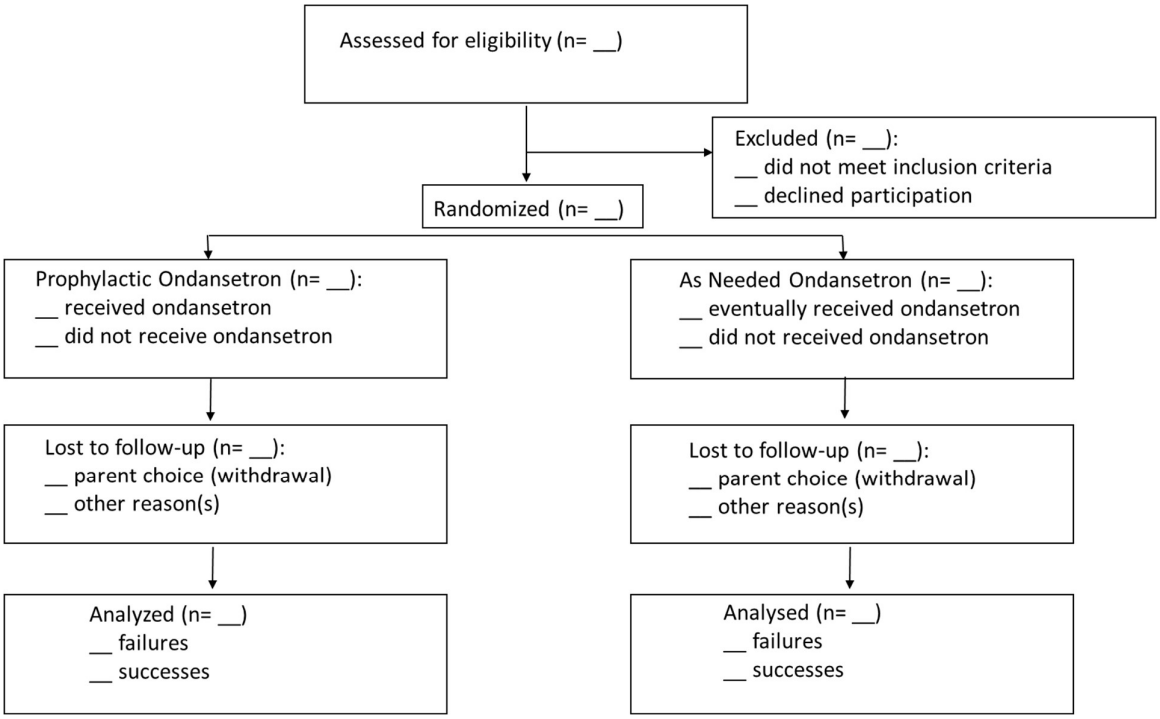

Figure 2: CONSORT flow diagram of trial participants.

9.2 Derived variables

Methotrexate intolerance is one of the two criteria used to determine patient failure during the trial. Intolerance is defined as ≥6 points in the English or French versions of the validated Methotrexate Intolerance Severity Score, MISS [1,2]. The MISS questionnaire is the sum of 12 items, each scored from 0 to 3, for a total possible score of 36 points. A derived variable named INTOLERANCE takes the value of 1 if a MISS score of 6 or more was ever recorded for a patient, or zero otherwise.

We determined weeks on trial as the number of weeks elapsed between the visit date and the date of enrolment in the trial.

9.3 Protocol Deviations

1. Patient exclusions: The primary analysis is an intention to treat analysis. As such, a randomized patient can only be excluded from the primary analysis in exceptional circumstances, such as the diagnosis of JIA proves to be wrong, or the patient was included in violation of the inclusion and exclusion criteria for the trial. For further clarity, a patient randomized to intervention cannot be excluded because they did not take ondansetron or because they withdrew from the trial. A patient randomized to control cannot be excluded because they took ondansetron or because they withdrew from the trial. To preserve the

integrity of an intention to treat analysis it thus follows that all randomized patients should have a value for the primary endpoint. Due to OPT-JIA study design with no fixed date visits and missing data, it was clear at the time of the interim analysis that there would be patients with no documented endpoint at 12 months. Instead of imputing the endpoint as failure for subjects with no documented endpoint at 12 months or having their last recorded information carried forward, it was decided to use Kaplan Meier estimates of the probability of success at 12 months as these account best for censored patients and missing information.

The secondary per protocol analysis will include all patients that received the assigned intervention for at least 3 months or who experienced intolerance within the first three months. For the intervention group this means the patient received methotrexate and prophylactic ondansetron for at least 3 months. For the control group this means the patient received methotrexate for at least 3 months. Patients that withdraw or are lost to follow-up before 3 months are not included in the per-protocol analysis, unless they already experienced intolerance or toxicity. Patients who withdraw or are lost to follow-up after 3 months will be considered censored and have their data analyzed using Kaplan Meier survival methods.

2. Analysis changes: Because the interim analysis would be based on a much smaller fraction of the intended sample size, the study PI and statistician proposed, and the DMC agreed, to base the interim analysis on the confidence interval for relative risk computed using the ratio of two estimates of the probability of successful trial completion from independently estimated Kaplan Meier curves. These estimates would better account for the partial information available from patients with incomplete information due to insufficient time in the study to complete the 52-week observation period. After it became clear during the interim analysis that some patients will not have a documented endpoint, it was decided that Kaplan Meier estimates will also be used in the final analysis.

9.4 Demographic and Baseline Variables

The following baseline variables will be used to describe the trial population:

Characteristic	Prophylactic ondansetron	As-needed ondansetron	Comments
Number of subjects			
Age at enrolment, median years (25^{th}, 75^{th} centiles)			
Female sex, number (%)			
Months since JIA diagnosis, median (25^{th}, 75^{th} centiles)			
JIA Category, number (%): Oligoarthritis RF-negative polyarthritis Enthesitis related arthritis Systemic arthritis Psoriatic arthritis RF-positive polyarthritis Undifferentiated			
Active joint count, median (25^{th}, 75^{th} centiles)			
Physician global, median (25^{th}, 75^{th} centiles)			
Parent global, median (25^{th}, 75^{th} centiles)			
C-reactive protein, median (25^{th}, 75^{th} centiles)			
Sedimentation rate, median (25^{th}, 75^{th} centiles)			
Weight group, number (%): <15Kg 15-30Kg >30Kg			
Previous treatment, number (%): None NSAID Joint injections Systemic corticosteroids DMARD Biologics Ophthalmic corticosteroids			
Known uveitis, number (%)			

9.5 Treatment Compliance

Compliance with ondansetron and methotrexate is queried at each medical visit by the attending physician (local investigator) and reported in the physician case report forms. Parents are asked to confirm in writing in the parents' questionnaire how many ondansetron tablets were given to their child with the previous dose of methotrexate.

Since this is a pragmatic trial to test effectiveness in usual medical practice, there will be no pill counts or measurement of blood medication levels as part of this trial.

10 Efficacy Analyses

The final efficacy analysis will be conducted after the last recruited trial participant has had an opportunity to be followed for 60 weeks from the date of recruitment (52 weeks plus an 8-week window of observation and data entry). The final dataset will then be verified and locked.

As per the OPT-JIA protocol (V3, 2-Sept-2020), the final analysis will be an intention to treat analysis including all randomized participants irrespective of whether they completed the trial, received or not the trial interventions, or dropped out. A secondary modified per-protocol analysis will be conducted on those subjects who received the assigned intervention for at least 3 months or stopped medications before 3 months for intolerance or toxicity.

All statistical analysis will test the null hypothesis of no differences between intervention and control groups. The a priori alternative hypothesis is that the intervention group will have better outcomes than the control group.

Logistic regression models will be used to adjust effect estimates for post-randomization imbalances in the two groups (intervention, control). Baseline variables with a p value <0.1 in the baseline comparison of intervention and control groups will be considered post-randomization imbalances and adjusted for, if any.

10.1 Primary Efficacy Analysis

The primary efficacy analysis is an intention to treat analysis comparing all subjects randomized to intervention to all subjects randomized to control. The primary efficacy analysis will include one primary endpoint and five secondary endpoints as described below.

Proportion of children who remain on methotrexate with no intolerance one year after starting methotrexate (Primary Endpoint): The primary endpoint (remain on methotrexate with no intolerance one year after starting methotrexate) has two components ("remain on methotrexate" and "no intolerance"). At every visit to the clinic the physician reports whether the patient is receiving methotrexate (MTX = 1) or not (MTX = 0). Temporarily not taking (holding) methotrexate due to intercurrent illnesses, running out of the medication, or similar reasons will not be considered a failure. If the reason for not taking methotrexate at one visit is unclear after review of the full record by the principal investigator, records will be verified with the site investigator. No intolerance means no MISS score of 6 or more points was ever recorded for that patient during the 52-week trial. Since the actual date the first methotrexate dose is given at home varies from family to family and it is not reliably recorded, we use the date of enrolment in OPT-JIA to calculate the 52 weeks of trial duration. Since OPT-JIA is a pragmatic trial and does not have study-specific visits, the visit

closest to 52 weeks is used, with a broad window of observation of 8 weeks before and 8 weeks after 52 weeks. To clearly differentiate between patients who dropped out and those who simply didn't have a visit on time, all available registry visits for all OPT-JIA participants will be provided to conduct the final analysis. Patients will be counted as successes rather than as censored if they have further registry visits beyond 52 weeks and had no failed before 52 weeks.

Our primary outcome statistic is the ratio of two proportions (relative risk, RR): the proportion of randomized children remaining on methotrexate with no intolerance one year after enrolment in the intervention group divided by the same in the control group. Subjects stopping ondansetron or methotrexate for toxicity or lack of efficacy will be counted as trial failures in calculations for the primary endpoint, irrespective of their MISS scores. A 95% CI for the RR will be calculated and the null hypothesis will be rejected if the confidence interval is entirely above 1. Considering that an interim analysis will be conducted, the alpha used in the final analysis will be 0.05 minus the alpha used in the interim analysis. As stated above, due to patient withdrawals and the fact that OPT-JIA did not have fixed-date visits, a number of patients was expected not to have a documented primary endpoint within the 52-week window, and a decision was made to use instead the Kaplan Meier estimates of the probability of success for calculations of the relative risk.

Cumulative incidence of methotrexate intolerance within one year: The Kaplan Meier survival analysis estimate of the cumulative incidence of a MISS score of 6 or more points within 52 weeks of study enrollment, as defined above. Kaplan-Meier curves will be constructed separately for intervention and control groups and the curves will be compared using the log-rank test.

Cumulative incidence of attainment of inactive disease within one year: The Kaplan Meier survival analysis estimate of the cumulative incidence of attainment of inactive disease within 52 weeks of study enrollment. At every visit to the clinic the pediatric rheumatologist is asked for current disease status (inactive disease = 1, active disease =2). Inactive disease is defined as per the Wallace criteria: no joints with active arthritis; no fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA; no active uveitis (by SUN definition, <1 cell in field sizes of 1 mm by a 1-mm slit beam); ESR or CRP level within normal limits in the laboratory where tested or, if elevated, not attributable to JIA [If not tested because there was no clinical indication, it is assumed to be normal]; physician's global assessment of disease activity (PGA) score of best possible on the scale used (0 in a 21 point scale from 0=inactive to 10=very active disease); duration of morning stiffness of 15 minutes or less. Additionally: no enthesitis. Active disease means any of the above disease manifestations is present, or a PGA of 0.5 or more. Kaplan-Meier curves will be constructed separately for intervention and control groups and the curves will be compared using the log-rank test.

Cumulative incidence of starting a biologic medication within one year: The Kaplan Meier survival analysis estimate of the cumulative incidence of starting a biologic medication within 52 weeks of study enrollment. At every visit to the clinic the physician is asked if the patient is receiving any biologic medication (Yes = 1, No = 0). If the answer is yes, the physician selects the relevant medication from a list or enters the name of the medication. Kaplan-Meier curves will be constructed separately for intervention and control groups and the curves will be compared using the log-rank test.

Mean quality of life scores in the Quality of My Life scale 4-8 months after starting methotrexate: The arithmetic mean of the score in the Quality of My Life scale answered by the patient. If more than one score is available 4-8 months after enrollment, the score closest to 26 weeks is used. All patients considered mature enough to understand the questions (by their parents) are asked: "Some

of the children who come to see us feel that their life is not that great, while others think that their life is O.K. How about you?" (The patient then selects the relevant answer in a 21-point horizontal rating scale from The worst = 0, to The Best = 10). Then, the patient is asked: "Considering my HEALTH, my life is..." and the patient again selects the relevant answer in a 21-point horizontal rating from The worst = 0, to The Best = 10). The answer to the second question is the score of interest. The mean scores of intervention and control groups will be compared with a two-sample two-tailed t-test.

Mean scores in the MISS questionnaire 4-8 months after starting methotrexate: The arithmetic mean of the score in the Methotrexate Intolerance Severity Score questionnaire answered by the parent. If more than one score is available 4-8 months after enrollment, the score closest to 26 weeks is used. The score is the sum of 12 items, each scored as 0= No complaints, 1= Mild, 2= Moderate, 3= Severe), for a total possible score of 36 points. The MISS questionnaire is included in the Case Report Forms appended to this Statistical Analysis Plan. The mean scores of intervention and control groups will be compared with a two-sample two-tailed t-test.

Mean scores and between groups p-values at 26 weeks are exploratory and will be interpreted with caution for two reasons: 1) OPT-JIA has no fixed-time visits and some patients may not have scores at 26 weeks; 2) The Quality of My Life score will not be available for patients deemed too young by their parents to understand the question.

10.2 Secondary Efficacy Analyses

There will be one secondary per-protocol efficacy analysis comparing all intervention and control subjects who received the assigned intervention for at least 3 months. The per-protocol analysis will be identical to the intention to treat analysis, except for the number of subjects included. For further clarity, it will consist of analyses of the same primary endpoint and five secondary endpoints, but only subjects that received the assigned intervention for 3 months will be included in comparisons. Because some patients may stop methotrexate due to intolerance before 3 months it was decided to conduct a modified per protocol analysis. The modified per-protocol analysis will include all patients receiving study medications for at least 3 months and all patients stopping medications before 3 months due to intolerance or toxicity. Physicians and parents are asked to report in separate case report forms if the patient is receiving ondansetron. If information is missing from one source, the other source will be considered true. If information is missing from both sources, the site investigator will be asked to verify ondansetron status against their clinical records.

11 Safety Analyses

OPT-JIA will assess the safety and tolerability of premedication with ondansetron, compared to as needed use. The safety endpoints are the frequency and cumulative incidence of adverse events and any serious unexpected suspected adverse drug reactions (SUSARs). Safety parameters in the OPT-JIA trial will be assessed using the standard set of questions about adverse events that are part of the CAPRI JIA Registry. These questions will be asked from the attending physician every time the study participant attends the pediatric rheumatology clinic for a medical visit. The form lists the following adverse events: abdominal pain, nausea/vomiting, rash (not JIA rash), injection reaction, infusion reaction, gastrointestinal bleed, abnormal blood counts, abnormal liver function tests, anaphylaxis, infection with hospitalization, tuberculosis, opportunistic infection, demyelinating disease, inflammatory bowel disease, malignancy, gastrointestinal perforation, eye surgery, joint surgery, and macrophage activation. Any non-listed events are reported as "Other / Not listed" by entering a description of the adverse event.

Frequency and cumulative incidence of adverse events: At every visit to the pediatric rheumatology clinic the rheumatologist is asked if an actionable adverse event has occurred since the previous visit (ADVERSE_EVENT = 1 if Yes, ADVERSE_EVENT = 0 if No). The physician then chooses the type of adverse event from the list of possible adverse events or enters the nature of the event if not listed. For each event, the physician reports what was done to address the event (additional visits, additional treatments, additional tests, hospitalization, surgery or change in anti-rheumatic medications). For each event, the physician reports if the event was serious. Actionable adverse event is defined as any untoward medical occurrence in a patient in the registry that requires additional medical visits, investigations, treatments, or a change in arthritis medications, **irrespective of its cause**. A serious adverse event is one that results in death, is life-threatening, requires hospitalization (admission for overnight stay), or results on a significant disability or a congenital anomaly. Or an adverse event that requires medical or surgical intervention to prevent dead, significant disability or a congenital anomaly.

Additionally, site principal investigators report directly to Health Canada and the study sponsor (Dr. Jaime Guzman) via fax any observed Serious Unexpected Suspected Adverse Drug Reactions (SUSARs) to Ondansetron within 24h of becoming aware of such occurrence, using the forms provided by Health Canada.

The final safety analysis will be conducted on the intention to treat population and consist of:

- A full listing of all the adverse events reported in the trial.
- A summary table comparing number and percentage of patients experiencing the most commonly reported adverse events in the intervention and control groups.
- The rates of adverse events for intervention and control groups calculated as number of events per 100 person-years of observation.
- The cumulative incidence of patients experiencing adverse events within 52 weeks in intervention and control groups, and 95% CI, calculated using Kaplan Meier survival methods.
- A figure showing the Kaplan Meier adverse event cumulative incidence curves for intervention and control groups within 52 weeks of enrolment.
- A comparison of the cumulative incidence curves for intervention and control groups using a log-rank test and reporting the corresponding p-value.

12 Other Analyses

In addition to estimates of intolerance-free survival and cumulative incidence of events, figures will show the corresponding Kaplan Meier curves from enrolment to 52 weeks with a table of subjects at risk in intervention and control groups at 10-week intervals underneath each figure.

13 Reporting Conventions

Medians and 25th, 75th centiles will be reported to one decimal place if applicable. Means and standard deviations for MISS scores and quality of life scores will be rounded to one decimal place. Time will be reported in full weeks throughout. Percentages will be rounded to 1 decimal place. P values will be reported to 3 decimal places. Any p values smaller than 0.001, will be reported as p<0.001. Kaplan Meier estimates of the probability of survival and cumulative incidence of events of interest will be reported as percentages with one decimal place.

14 Quality Assurance of Statistical Programming

The OPT-JIA interim and final statistical analyses will be conducted by the PhD student Matt Berkowitz and the results and statistical code will be verified by Professor Tom Loughing.

All final statistical code and outputs will be filed in the OPT-JIA files at the BC Children's Hospital network computer servers.

Any outputs will have the

- date and time included
- the name of the code file that produced the analysis
- the author

At the start of any code file there will be a set of comments that give

- the author
- the date and time of writing
- references to inputs and outputs
- reference to any parent code file that runs the child code file

15 Summary of Changes to the Statistics

Changes to the statistical analysis outlined in the OPT-JIA protocol V3, September 2, 2019, concerned primarily the interim analysis (described in the following paragraphs). There were no changes to the 6-monthly safety analyses. The changes of note for the final efficacy analysis were the use of Kaplan Meier estimates to allow for patients with incomplete follow-up and calculate the risk ratio, and the use of a modified per protocol analysis that included participants who stopped medications before 3 months because of intolerance or toxicity.

With the agreement of the Steering Committee and the Data and Safety Committee, the interim analysis took place at an earlier stage than initially specified because of the slow enrolment into the study. The interim analysis was planned by Professor Tom Loughin with the assistance of Matt Berkowitz and discussed with the PI, Dr. Jaime Guzman, in March 2023. It was discussed and approved at the steering committee call of April 21, and at the Data and Safety Committee call on May 8, 2023, and further confirmed with the DSC chair via email on October 5, 2023. The approved plan was to extract information from the REDCap database on September 30, and this was postponed to October 6, to allow time for responses to remaining queries to be verified by site principal investigators. The sample sizes for the interim analysis were smaller than had been expected, and hence there were only 27 patients on whom success or failure had been definitively determined at the time the interim analysis was conducted with data extracted on October 6th, 2023. There were an additional 17 participants who were still on the trial, with at least one follow-up visit but not yet to their 52-week visit. We therefore used the Kaplan-Meier (KM) statistical analysis technique separately in each group to estimate the probability of success in each group in a way that would make some use of the partial information provided by the patients with incomplete follow-up periods.

We used the KM method to estimate the probability of success at 52 weeks and formed the relative risk (RR) by dividing the estimated probability for the intervention group by the estimated probability for the control group. The statistical properties of the RR are better expressed on the log scale, so we computed the log of this ratio, which is equivalent to the difference between the two logged survival probabilities. We computed the standard error for this difference using the separate standard errors for each logged survival probability and computed the confidence interval on this log scale using the standard normal (Wald) method. The same KM methods will be applied for the final efficacy analysis.

According to the O'Brien-Fleming alpha-spending rule [17], we used alpha=0.0045 for the interim analysis rather than 0.05 so that we would maintain maximum power in the final analysis while controlling the probability of falsely discovering a difference between the two treatments if there is none. Once the confidence interval was computed on the log scale, we exponentiated the two endpoints to transform it into the original relative-risk scale. These are standard techniques described, for example, in books on survival analysis [20].

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16 Listing of Tables, Listings and Figures

The 6-monthly Safety reports include:

- A Table 1 comparing baseline characteristics of intervention and control participants.
- A Table 2 listing all observed adverse events.

The Interim Analysis report includes:

- A Table 1 comparing baseline characteristics of intervention and control participants.
- A Table 2 listing efficacy outcomes to date in the intervention group.
- A Table 3 listing efficacy outcomes to date in the control group.
- A Table 4 listing all observed adverse events.
- A Figure 1 showing patient disposition organized as per the CONSORT statement.
- A Figure 2 showing Kaplan Meier survival curves for intolerance free survival for intervention and control groups.

The final Analysis Report includes:

- A Table 1 comparing baseline characteristics of intervention and control participants.
- A Table 2 listing efficacy outcomes in the intervention group.
- A Table 3 listing efficacy outcomes in the control group.
- A Table 4 summarizing efficacy outcomes in intervention and control groups in side-by-side columns, with p values for the comparisons.
- A Table 5 listing all observed adverse events.
- A Table 6 comparing adverse events in intervention and control groups.
- A Figure 1 showing patient disposition organized as per the CONSORT statement.
- A Figure 2 showing Kaplan Meier survival curves for intolerance free survival for intervention and control groups.
- A 4-panel Figure 3 showing cumulative incidence curves for methotrexate intolerance, attainment of inactive disease, starting biologic medications, and experiencing an adverse event.

The manuscript for publication includes:

- A Table 1 comparing baseline characteristics of intervention and control participants.
- A Table 2 comparing efficacy outcomes in intervention and control groups and p values for the comparisons.
- A Table 3 comparing adverse events in intervention and control groups.
- A Figure 1 showing patient disposition organized as per the CONSORT statement.
- A Figure 2 showing Kaplan Meier survival curves for intolerance free survival for intervention and control groups
- A 4-panel Figure 3 showing cumulative incidence curves for methotrexate intolerance, attainment of inactive disease, starting biologic medications, and experiencing any adverse event.

Although tables and figures are numbered differently within each report, for the sake of making each report stand on their own, the format of tables and figures that are repeated across reports will be consistent. The following pages show the corresponding mock tables and figures, numbered according to the final analysis report.

Table 1: Baseline characteristics of patients recruited into the OPT-JIA trial

Characteristic	Prophylactic ondansetron	As-needed ondansetron	P-value
Number of subjects			
Age at enrolment, median years (25^{th}, 75^{th} centiles)			
Female sex, number (%)			
Months since JIA diagnosis, median (25^{th}, 75^{th} centiles)			
JIA Category, number (%): Oligoarthritis RF-negative polyarthritis Enthesitis related arthritis Systemic arthritis Psoriatic arthritis RF-positive polyarthritis Undifferentiated			
Active joint count, median (25^{th}, 75^{th} centiles)			
Physician global, median (25^{th}, 75^{th} centiles)			
Parent global, median (25^{th}, 75^{th} centiles)			
C-reactive protein, median (25^{th}, 75^{th} centiles)			
Sedimentation rate, median (25^{th}, 75^{th} centiles)			
Weight group, number (%): <15Kg 15-30Kg >30Kg			
Previous treatment, number (%): None NSAID Joint injections Systemic corticosteroids DMARD Biologics Ophthalmic corticosteroids			
Known uveitis, number (%)			

Table 2: Intervention Group Outcomes

Table 2: Intervention Group Outcomes										
ENROL DATE	CAPRI_ID	WEEKS of FU	Failure	On MTX at FU	Intolerance ever	Ondansetron ever	Biologic at FU	Active at FU	MISS 4-8m	HRQoL 4-8m
9/6/2019	00000	58	Yes	No	Yes	Yes	Yes	Yes	5	39
Totals	N=__	Median (25th,75th)	n_ (%)	n (%)	n (_%)	n (_%)	n (_%)	n(_%)	mean (SD)	mean (SD)

Table 3: Control Group Outcomes

Table 3: Control Group Outcomes										
ENROL DATE	CAPRI_ID	WEEKS of FU	Failure	On MTX at FU	Intolerance ever	Ondansetron ever	Biologic at FU	Active at FU	MISS 4-8m	HRQoL 4-8m
9/6/2019	00000	58	Yes	No	Yes	Yes	Yes	Yes	5	39
Totals	N=__	Median (25^{th},75^{th})	n_ (%)	n (%)	n (_%)	n (_%)	n (_%)	n(_%)	mean (SD)	mean (SD)

Table 4: Primary and secondary outcomes in intervention and control groups

Outcome	Intervention	Control	Relative risk (95% CI)	p-value
On methotrexate with no intolerance	n (%)	n (%)	__ (__, __)	0.001
Methotrexate intolerance	n (%)	n (%)		
Inactive disease	n (%)	n (%)		
On biologic medication	n (%)	n (%)		
Mean MISS scores at 4-8m	mean (SD)	mean (SD)	mean difference (CI)	0.001
Mean quality of life scores at 4-8m	mean (SD)	mean (SD)	mean difference (CI)	

Alternatively, numbers for MTX intolerance, inactive disease and biologic medication could report Kaplan Meier estimates of the cumulative incidence at 52 weeks with CI.

Table 5: All observed adverse events in the OPT-JIA trial

Subject ID	**Enrol date**	**Visit date**	**Study arm (Prophylactic / As needed)**	**Route of MTX (Oral/SQ)**	**Medications at time of the event**	**Event**	**Actions**	**Serious (Yes / No)**	**Related to ondansetron**
_____	27/Aug/19	26/Nov/19	A	SQ	MTX Naproxen Folic acid	Infection	Hospital Additional treatment	Yes	No

Table 6: Most frequent adverse events in Intervention and Control Groups

Adverse event	Intervention (N=__)	Control (N=__)	p-value
Abdominal pain	n (_%)	n (_%)	0.001
Nausea/vomiting			

Numbers are the number (%) of patients experiencing that adverse event at least once during the trial.

Figure 1: CONSORT flow diagram of trial participants.

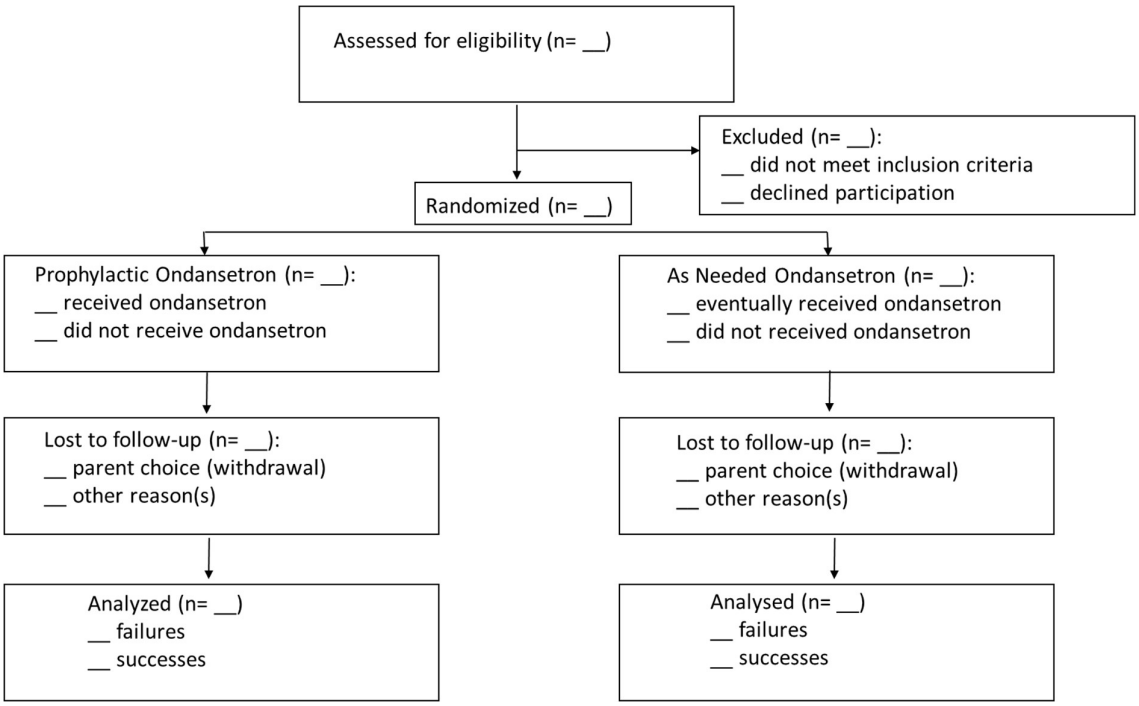

Figure 2: Kaplan Meier survival curves of the probability of being on methotrexate without intolerance for intervention and control groups.

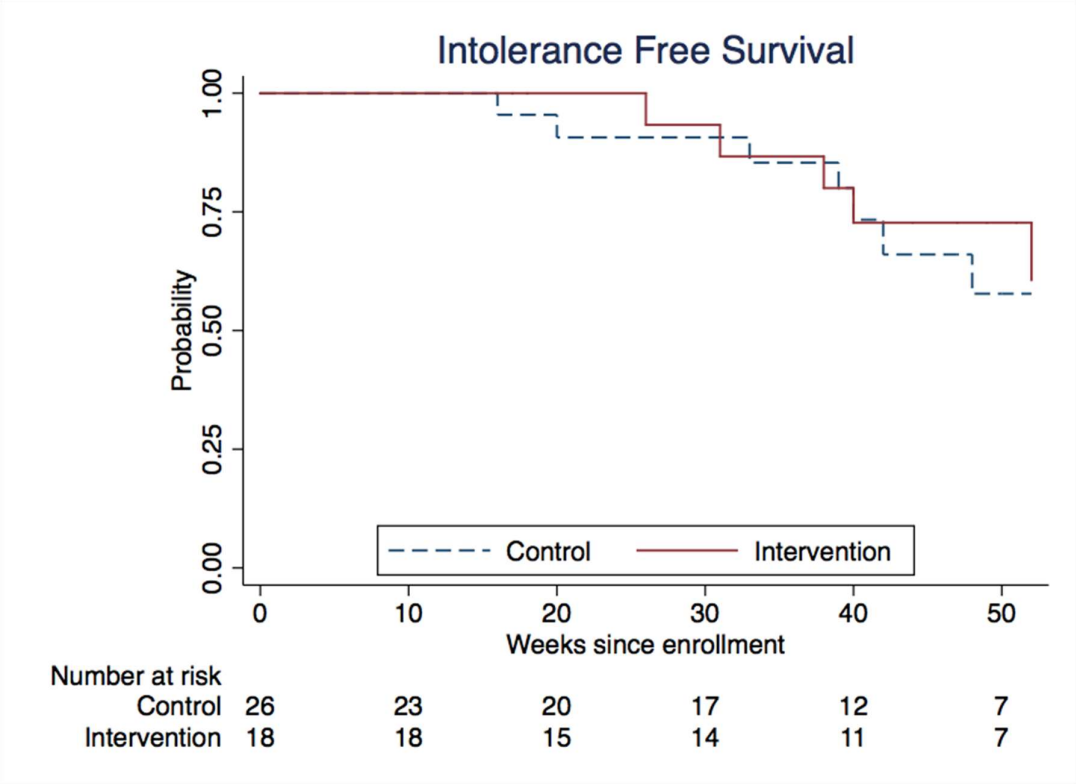

Figure 3: Cumulative incidence curves in intervention and control groups for A) methotrexate intolerance, B) attaining inactive disease, C) starting a biologic agent, D) developing an adverse event.