1.0 Title Page

REGISTRY PROTOCOL P10-262

A Long-term, Multi-center, Longitudinal Post-marketing, Observational Registry to Assess Long-term Safety and Effectiveness of HUMIRA® (Adalimumab) in Children with Moderately to Severely Active Polyarticular or Polyarticular-course Juvenile Idiopathic Arthritis (JIA) - *STRIVE*

Incorporating Administrative Changes 1, 2, 3, 4, and 5 and Amendments 1, 2, 3, 4, 5 and 6

Investigational Product:	Humira® (adalimumab)
Type of Registry:	A Post-Marketing, Observational Registry; Post-Authorization Safety Study
Date:	05 April 2016
Physicians:	Multicenter Registry (Physician information on file at AbbVie)
Sponsor:	AbbVie 1 North Waukegan Road North Chicago, IL 60064-6146 USA
AbbVie Emergency Contact:	[redacted]
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This registry will be conducted in compliance with the protocol.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Update AbbVie Study Designated Physician/Emergency Contact details.

  Rationale: *Reflect current AbbVie personnel information.*
- Address inconsistencies throughout the protocol.
- Incorporate Administrative Change 4 regarding pregnancy reporting.

  Rationale: *Clarify the data collection period for pregnancies to be from the date of the first dose of registry drug through 150 days following the last dose of registry drug or the end of the patient's participation in the registry (whichever is longer).*
- Incorporate Administrative Change 5.
- Make a global update to the document from "JIA" to "polyarticular JIA" when referring to the Humira approved indication and patient population in this registry.

  Rationale: *Clarified the subtype of JIA as "polyarticular" JIA throughout the document.*
- Section 3.0, Introduction:
  - Update with the most current approval dates for Humira.

  Rationale: To reflect the most updated and accurate information.
- Implement a new standard process for the collection of Product Complaints, by creating Section 7.0, Complaints.

  Rationale: *Comply with new AbbVie standards.*
- Section 3.0, Introduction:
  - Update that Actemra®/RoActemra® (tocilizumab) was approved for treatment of polyarticular JIA in US and EU in 2013.
  - Update that Ilaris (canakinumab) was approved for treatment of systemic JIA in EU and US in 2013.
  - Update that Humira is now approved in over 90 countries worldwide for at least one indication.

- Update that polyarticular JIA is approved in over 80 countries.
- Update that Humira is approved for the treatment of patients with early RA, polyarticular JIA (2 years of age and older), PsA, ankylosing spondylitis (AS), Crohn's disease (CD) (adult and pediatric), ulcerative colitis (UC), plaque psoriasis (plaque Ps) (adult), and hidradenitis suppurativa (HS).
- Update that adalimumab is also approved for the treatment of patients with pediatric ERA, pediatric plaque Ps, and non-radiographic axial spondyloarthritis (nr-axSpA) in the EU and several other countries, as well as for intestinal Behçet's disease (BD) in Japan, Argentina, Korea, and Taiwan.

Rationale: *To reflect the most updated and accurate information.*

- Section 4.0, Rationale:
  - Update that Humira is approved in the US for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

    Rationale: *Update Humira approvals for patients 2 years of age and older.*
  - Update that in the EU Humira in combination with methotrexate (MTX) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

    Rationale: *Update Humira approvals for patients 2 years of age and older.*
  - Clarify that patients will be followed for up to 10 years in either treatment arm.

    Rationale: *To allow for patient follow up for up to 10 years in either treatment arm.*
- Section 6.0, Investigational Plan:
  - Clarify that all SAEs and AESI, not only treatment emergent SAEs and AESI, will be collected for the full 10 years.

Rationale: *To allow for the collection of all SAEs and AESI for the full 10 years.*

- Clarify that starting at Year 6, patients will be followed annually for SAEs, a subset of AESI that includes congestive heart failure, malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies through Year 10.

  Rationale: *Added language to clarify that patients will be followed annually starting at Year 6.*

- Section 6.1, Selection of Population:
  - Delete statement, "Patients in the JIA registry in the U.S. may also be co-enrolled in the AbbVie sponsored Humira pediatric injection site pain study which includes a new formulation of adalimumab. Collection of safety information for patients that are co-enrolled in the JIA registry and the AbbVie Humira pediatric injection site pain study are described in Section 6.6.5."

  Rationale: *Planned Humira pediatric injection site pain study was cancelled.*

- Section 6.5, Registry Duration:
  - Delete sections and moved them to Section 6.6.5, Safety Data Collection and Section 7.1.7, Adverse Event Collection Period.

  Rationale: *Moved sections in the protocol to allow for new sections to be added.*

- Section 6.6, Registry Conduct:
  - Update section with statement, "For collection of Safety data see Figure 1 and Figure 2."
  - Update/clarify Figure 1, Registry Schematic for Polyarticular JIA Patients 4 to 17 Years of Age, for Years 6 – 10.

    Rationale: *Added language to clarify Figure 1 and Figure 2.*
  - Update, Table 1, Registry Activities, table note "f."

    Rationale: *Added language to clarify safety data being collected.*

- Section 6.6.4, Prior and Concomitant Medications:

- Clarify that during registry participation, patients should not be enrolled in any interventional clinical trial.

  Rationale: *Patients were previously allowed to be coenrolled in the Abbott sponsored Humira pediatric injection site pain study. This study has since been cancelled.*

- Section 6.6.5, Safety Data Collection:
  - Clarify that safety information will be collected from the time the patient consent and/or patient assent forms are signed.

    Rationale: *To change the language from "patient" consent to "parental" consent.*
  - Paragraphs addressing safety data that is collected during the first 5 years and in the last 5 years were moved from Section 6.5, Registry Duration, to Section 6.6.5, Safety Data Collection.

    Rationale: *Moved sections in the protocol to allow for new sections to be added.*
  - Information about the HCP process and safety data collected during the HCP process was moved Section 6.5, Registry Duration, to Section 6.6.5, Safety Data Collection.

    Rationale: *Moved sections in the protocol to allow for new sections to be added.*
- Section 6.6.6, Physician Global Assessment and Patient Reported Outcome Measurements:
  - Update the name of the Patient Reported Outcome (PRO) to read Parent's Global Assessment of patient's disease activity.

    Rationale: *Updated into accurate PRO.*
- Section 6.6.7, Joint Assessment:
  - Add reference to Appendix D, Pediatric Total Joint Assessment.
- Section 6.7.1, Effectiveness Variables:
  - Update the names of the following PROs:
    - Parent's Assessment of Patient's Pain (VAS).
    - Parent's Global Assessment of Patient's Disease Activity.

Rationale: *To reflect accurate title of the PROs.*

- Clarify the names of the following assessments:
  - Number of joints with limitation of passive motion (LOM).
  - Number of joints with pain on passive motion (POM).

  Rationale: *Added the word "passive" for clarity of assessment.*

- Section 6.7.2, Safety Variables:
  - Clarify that if treatment with Humira or MTX is permanently discontinued for any reason, patients will be discontinued from treatment and the reason for discontinuation will be recorded on the Study Drug Completion eCRF
  - Clarify that SAEs, AESI and pregnancies will be collected on their respective eCRFs.

    Rationale: *Added language to clarify which forms are used to collect this information.*

- Section 7.7.1, Adverse Events/Adverse Events of Special Interest Reporting:
  - Clarify that patients will be monitored for all Adverse Events from the time the parental informed consent/patient assent form is signed throughout registry participation.

    Rationale: *To change the language from "patient" consent to "parental" consent.*
  - Clarify that all events will be followed until a satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

    Rationale: *To comply with AbbVie standard language*

- Section 7.1.7, Adverse Event Collection Period:
  - Clarify that SAEs, AESI and pregnancies can be collected throughout the study, not only at doctor visits.

    Rationale: *To ensure collection of SAEs, AESI and pregnancy at any time during the registry.*
  - Paragraphs addressing safety data that is collected during the first 5 years and in the last 5 years were moved from Section 6.5, Registry Duration to Section 7.1.7, Adverse Event Collection Period.

Rationale: *Moved sections in the protocol to allow for new sections to be added.*

- Remove sentence relating to HCP Process and collection of Safety Data on an annual basis, which is identified as being repetitive.

- Section 7.1.8, Serious Adverse Event Reporting:
  - Clarify that physicians should report SAEs and nonserious events of malignancy in patients 30 years and younger whether related to registry drug or not to AbbVie Clinical Pharmacovigilance.
  - If the EDC system is not operable, SAEs and nonserious events of malignancy in patients 30 years and younger should be documented on the SAE Non-CRF paper forms and emailed or faxed to AbbVie Clinical Pharmacovigilance within 24 hours of the site's awareness of the SAE.
  - Update the new fax number for AbbVie Clinical Pharmacovigilance.
  - Update the email address for paper CRFs to be sent to AbbVie Clinical Pharmacovigilance.

    Rationale: *To update AbbVie departmental name change from AbbVie Immunology Clinical Safety Management Team to AbbVie Clinical Pharmacovigilance.*
  - Clarify the Immunology Safety Team Department number.

    Rationale: *To update Immunology Safety Team Department number*.
  - Clarify that for safety concerns, the Primary Study Designated Physician should be contacted. Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, a central back-up phone number is provided.

    Rationale: *To update central back-up phone number.*
- Section 7.1.9, Pregnancy, Pregnancy in a registry patient must be reported to AbbVie (see contact details in Section 7.1.8, Serious Adverse Event Reporting) within 1 working day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected. Pregnancies will be collected from the date of the first dose through 150 days following the last dose of registry drug or the end of registry (whichever is longer).

Rationale: *To comply with current standard AbbVie procedures.*

- Section 7.1.9, Pregnancy:
  - Clarify that pregnancies will be collected from the date of the patient's first dose of the registry drug through 150 days following the last dose or the end of the patient's participation in the registry (whichever is longer).

    Rationale: *To comply with current AbbVie procedures.*
- Section 7.3, Data Collection Procedures for Patients Who Participate in the Direct to HCP Process:
  - For patients participating in the direct to HCP process, HCPs will document any Adverse Event of Special Interest, hospitalizations, surgeries, and death as defined in Section 7.1.2, Adverse Event Definition, on an annual basis via a paper questionnaire or eCRF through the first 5 years of the patient's enrollment date in the registry.
  - Clarify that HCPs will document any occurrence of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death annually via a questionnaire or eCRF beginning at Year 6 through Year 10.

    Rationale: *To comply with current AbbVie procedures.*
- Section 8.1, Quality Assurance:
  - Clarify that at least one monitoring visit will be performed at each site for the duration of the study.

    Rationale: *Added "at each site" rather than a subset of sites.*
  - Clarify that during the monitoring visit, entries on the eCRF are reviewed against source documents to verify accuracy and appropriate completion of the eCRF.

    Rationale: *To ensure accuracy of eCRFs that are reviewed against source documents.*
  - Clarify AbbVie's involvement (if needed) in site follow-up.

    Rationale: *To clarify that AbbVie's involvement is on an "as needed" basis for site follow-up.*
  - Clarify that all paper questionnaires will be reviewed for completion by the site or by the CRO (as appropriate) prior to entry into database.

Rationale: *Clarified that all paper questionnaires must be completed prior to database lock.*

- Section 9.0, Case Report Forms and Source Documents:
  - Clarify the names of the following PROs:
    - Parent's Global Assessment of Patient's Disease Activity (VAS).
    - Physician Global Assessment of Disease Activity (VAS).
- Section 10.2, Demographics and Registry Enrollment Characteristics:
  - Clarify that for patients who rolled over from Study DE038 and were in placebo arm during double-blind period of this study, that the duration of the double-blind period will be subtracted from total exposure.

    Rationale: *Clarified that duration of placebo treatment from Study DE038 is not included in the total exposure calculation.*
- Section 10.3, Safety Analyses:
  - Clarify that for patients enrolled from Study M10-444 and Study DE038 that the total SAEs and AESI will include events reported after the first recorded dose of study drug in the previous study, except those which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period, any events reported by retrospective data collection, and events reported during this registry.

    Rationale: *Clarified handling of SAE/AESI occurring during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period.*
  - Clarify that registry treatment-emergent AEs exclude AEs during treatment interruptions.

    Rationale: *Clarified definition of registry treatment-emergent AEs.*
- Section 10.3.1, Analysis of Observational SAEs and AEs of Special Interest:
  - Clarify that rates (event per 100 patient year of observation) of SAEs and AEs of Special Interest and the 95% confidence interval will be provided.

    Rationale: *Clarified that confidence intervals will be provided for rates (event per 100 patient year of observation) of SAE/AESI.*

- Clarify that summaries provided will use the data from first day in registry through the last contact irrespective of drug treatment duration.

  Rationale: *Clarified data will be included from first day in registry.*

- Section 10.3.2, Analysis of Registry Treatment-Emergent SAEs and AEs of Special Interest.
  - Clarify that registry treatment-emergent AEs exclude AEs during treatment interruptions.

    Rationale: *Clarified definition of registry treatment-emergent AEs.*

- Section 10.3.3, Analysis of All Treatment-Emergent SAEs and AEs of Special Interest:
  - Clarify that AEs which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period will be excluded from analysis.

    Rationale: *Clarified handling of SAE/AESI occurring during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period.*

  - Clarify that all treatment-emergent AEs exclude AEs during treatment interruptions.

    Rationale: *Clarified definition of all treatment-emergent AEs.*

- Section 10.4.1, Juvenile Idiopathic Arthritis Core Set of Variables:
  - Update "patient's disease severity" to "patient's disease activity."
  - Update the scoring of the PRO Parent's Global Assessment of patient's disease activity (very well – very bad) so that "0 = very good" is updated to "0 = very well."

    Rationale: *Updated into accurate scoring.*

  - Clarify number of active joints with limitation of passive motion (LOM).

    Rationale: *Clarified the number of active joints for the core set of variables.*

- Section 10.4.1.1, Definition of PedACR30 Response:
  - Update statement to read that the improvement of a core set of variables by ≥ 30% is defined as a percent change from Baseline less than equal to

–30% and worsening of a core set of variables by ≥ 30% is defined as a percent change from Baseline greater than or equal to 30%.

Rationale: *Correction of typographical error.*

- Section 10.4.1.3, Definition of JADAS:
  - Clarify the names of the following PROs:
    - Physician's Global Assessment of Patient's Disease Severity to Disease Activity.
    - Parent's Global Assessment of patient's overall well being to Disease Activity.

      Rationale: *Updated into accurate PRO's title.*
  - Clarify that Normalized ESR or CRP if collected and available only when part of the physician's site routine care.

    Rationale: *Clarified that the collection of ESR or CRP is part of the physician's site routine care.*
- Section 10.4.1.4, Other Analyses:
  - Clarify for patients being enrolled from AbbVie clinical Study DE038 or Study M10-444, baseline will be defined as the last non-missing observation on or before the date of enrollment in the registry since these assessments were not collected in Study DE038 or not collected in Study M10-444 or not collected in both studies.

    Rationale: *Clarified baseline derivation for patients from Studies M10-440 and DE038.*
- Section 10.5, Interim Analyses:
  - Clarify that the effectiveness analyses may also be included in the Interim Reports as deemed appropriate.

    Rationale: *Clarified reporting of effectiveness data within interim analyses.*
- Section 14.0, Reference List:
  - Add reference: Kingsbury DJ, Bader-Meunier B, Patel G, et al. Safety, effectiveness, and pharmacokinetics of adalimumab in children with

polyarticular juvenile idiopathic arthritis aged 2 to 4 years. Clin Rheumatol. 2014;33(10):1433-41.

Rationale: *Added reference on use of Humira in children ages 2 to < 4 with polyarticular JIA.*

- Appendix A, List of Abbreviations and Definition of Terms:
  - Add Abbreviation: AESI (Adverse Events of Special Interest).

    Rationale: *Abrreviation of AESI was added to the protocol.*
  - Clarify LOM (Limitation of Passive Motion).
  - Clarify POM (Pain on Passive Motion).

    Rationale: *Added "passive" for clarity.*
- Appendix B, List of Protocol Signatories:
  - Update list of signatories for the protocol.

    Rationale: *To reflect correct AbbVie personnel.*

An itemized list of all protocol changes made to this amendment can be found in Appendix I.

2.0 Table of Contents

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3.0 Introduction

Juvenile idiopathic arthritis (JIA), an autoimmune disease with clinical onset before 16 years of age and with a complex genetic predisposition, is one of the most common autoimmune musculoskeletal diseases of childhood. This important cause of disability in children and adolescents has an estimated incidence of 15 per 100,000 and is 2.5 times more common in females.[1] The incidence data were derived primarily from North American and European populations.

Current classification of JIA accepted internationally is the second revision of the International League of Associations for Rheumatology (ILAR). The ILAR classification identifies the following 7 subcategories of JIA based on the number of joints affected and the presence or absence of serologic findings and systemic manifestations: systemic arthritis, polyarthritis (sero-positive and sero-negative), oligoarthritis (persistent and extended), enthesitis-related arthritis (ERA), psoriatic arthritis (PsA), and undifferentiated arthritis.[2]

The onset of JIA is characterized by three primary modes: Oligoarthritis (< 5 joints) is the most frequent in 50%; polyarticular (≥ 5 joints) in 30%; and systemic arthritis (at least one joint with fever and rash) in 10% to 20% of patients.[3]

Nonsteroidal anti-inflammatory agents (NSAIDs) are the usual first line treatment for JIA, since they are considered to be the least toxic agent in children. NSAIDs provide symptomatic relief, but are not considered to be disease modifying.[4] NSAIDs are often used in conjunction with disease-modifying antirheumatic drug (DMARDs) such as methotrexate (MTX) or sulfasalazine. MTX is considered to have an acceptable level of toxicity relative to its efficacy; most children demonstrate at least some response to MTX therapy although remission is rare. After starting MTX, the onset of response usually ranges from 3 to 6 months.[5,6] Many children have a disease relapse after withdrawal of MTX.

Other types of traditional medications commonly used to treat RA in adults are less acceptable for use in pediatric patients. Cytotoxic drugs have unacceptable risk in children, since they are known to be both immunosuppressive and mutagenic. Systemic corticosteroids promote susceptibility to infections, osteoporosis and growth disturbance and have not been shown to be disease-modifying in children.

More treatments based on new technologies are becoming available for the treatment of JIA. Cytokines, hormone-like proteins that allow cells to communicate, play critical roles in normal biologic processes, such as cell growth, inflammation and immunity.[7]

Two inflammatory cytokines, tumor necrosis factor alpha (TNF- α) and interleukin (IL)-1, are critical in the progression of inflammatory synovitis and articular matrix degradation, and therefore represent promising targets for therapeutic intervention in RA.[8,9] When TNF is inhibited; the levels of other pro-inflammatory cytokines are also reduced, such as IL-1 and IL-6. The clinical and immunopharmacological profiles of anti-TNF therapy suggest that TNF inhibition is well-tolerated and provides long lasting clinical benefit, including the prevention of structural joint damage for patients with RA.[10,11]

TNF-α has been noted to be elevated in serum, synovial fluid, and synovial tissue of children with polyarticular JIA[11,12] and therefore represents a promising target for the therapeutic management of polyarticular JIA. Clinical trials using agents that block TNF activity demonstrate the central role for this cytokine in the pathogenesis of RA and other autoimmune diseases.[7] The most common strategies to neutralize TNF-α are through the administration of soluble TNF receptor molecules or monoclonal antibodies to TNF. A double-blind, placebo, controlled withdrawal study in children with polyarticular JIA refractory to MTX provided evidence of short-term effectiveness and safety for treatment with Enbrel® (etanercept), a soluble TNF receptor p75 fusion protein.[13] Enbrel® (etanercept) was approved in the United States (US) and the European Union (EU) for the use in polyarticular JIA patients in 1999 and 2000, respectively. A randomized, double blind, placebo controlled withdrawal study in children with polyarticular JIA provided evidence of efficacy and safety for treatment with Orencia® (abatacept), a selective T-cell

co-stimulation modulator.[14] Orencia® (abatacept) was approved for the treatment of polyarticular JIA in the United States (US) in 2008 and in the EU in 2010.

Actemra®/RoActemra® (tocilizumab) was approved for the treatment of systemic JIA in Japan in 2008 and in the EU and US in 2011, and was approved for treatment of polyarticular JIA in the EU and US in 2013.

Ilaris (canakinumab) is approved for treatment of systemic JIA in the EU and US in 2013.

Humira is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Humira is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons. Humira is composed of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Humira binds with high affinity and specificity to soluble TNF-α but not to lymphotoxin-α (TNF-β).

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. Humira binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Humira also modulates biological responses that are induced or regulated by TNF. After treatment with Humira, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease.

Humira was first approved for the treatment of patients with RA in the US in December 2002 and in the EU in September 2003. In addition, adalimumab is approved for the treatment of patients with polyarticular JIA (2 years of age and older), early RA, PsA, ankylosing spondylitis (AS), Crohn's disease (CD) (adult and pediatric), ulcerative colitis (UC), plaque psoriasis (plaque Ps) (adult), and hidradenitis suppurativa (HS) in the EU, US, and the rest of the world. Adalimumab is also approved for the treatment of

patients with pediatric ERA, pediatric plaque Ps, and non-radiographic axial spondyloarthritis (nr-axSpA) in the EU and several other countries, as well as for intestinal Behçet's disease (BD) in Japan, Argentina, Korea, and Taiwan. As of 31 December 2015, Humira has been approved for at least one indication in over 90 countries worldwide (polyarticular JIA is approved in over 80 countries).

Key data of the pre-clinical toxicology, metabolism, and pharmacology can be found in the Humira labeling. In addition, a randomized, double-blind, placebo-controlled withdrawal study in children ages 4 to 17 with polyarticular JIA and an open-label study in children (2 to < 4 years old or aged 4 and above weighing < 15 kg) with polyarticular JIA provided efficacy and safety data with Humira.[13,15] The consolidated safety data are summarized in the Humira label. Refer to the most current local Humira label for a summary of DE038 and a comprehensive presentation of the safety information.

The great majority of information is coming from adult RA patients treated with Humira.

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. Tuberculosis (TB) has also been observed in subjects treated with TNF antagonists, including Humira.

TNF antagonists, including Humira, have been associated with cases of demyelinating disease. Serious allergic adverse reactions have been reported in subjects following subcutaneous administration of Humira.

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma and non-melanoma skin cancer have been observed among patients receiving a TNF-antagonist compared with control patients. The size of the control group and limited duration of the controlled portions of studies precludes the ability to draw firm conclusions. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which

complicates the risk estimation.[14-17] In the Humira JIA Studies DE-038, M10-240 and M10-444 no malignancy has been observed in the total number of 228 patients enrolled.

Very rare post marketing reports of hepatosplenic T-cell lymphoma (HSTCL), a rare aggressive lymphoma that is often fatal, have been identified in patients treated with Humira. Most of the patients had prior infliximab therapy as well as concomitant azathioprine or 6-mercaptopurine use for Crohn's disease. The causal association of HSTCL with Humira is not clear.

Malignancies, some fatal, have been reported among children and adolescents who received treatment with TNF-blocking agents. Most of the patients were receiving concomitant immunosuppressants. These cases were reported post-marketing and are derived from a variety of sources including registries and spontaneous postmarketing reports.

The risk of malignant melanoma has been report to be increased in patients with a medical history of extensive immunosuppressant therapy.[19]

There have also been cases of acute and chronic leukemia reported in association with the use of TNF-antagonists including Humira. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

No studies have been conducted that include patients with a history of malignancy other than a successfully treated non-metastatic cutaneous squamous cell and/or basal cell carcinoma and/or localized carcinoma in situ of the cervix. Further, there are no data currently available on subjects who develop malignancy while receiving Humira and subsequently continue treatment. Thus additional caution should be exercised in considering Humira treatment in these patients.

3.1 Safety Information

In 2008, the FDA issued an early communication about an ongoing safety review of TNF blockers and the development of lymphoma and other cancers in children and adolescents.

As of the December 2009 FDA Pediatric advisory committee, it was noted that in general, adverse events seen in studies submitted for the JIA indication were similar to those in the adult population, both in type and frequency.

Due to the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers, the FDA was unable at that time to fully characterize the strength of the association between using TNF blockers and developing a malignancy. Product labeling for all anti-TNF agents now includes language regarding the risk of pediatric malignancies as requested by the FDA.

Furthermore, in November 2011 the FDA requested that all manufacturers of TNF inhibitors undertake a coordinated effort to better understand the risks for malignancies that develop in patients who are 30 years of age and younger at the time of diagnosis. Reporting requirements for these events can be found in Section 7.1.8 Serious Adverse Event Reporting. A detailed discussion of the clinical toxicology, metabolism, pharmacology, and safety experience with adalimumab can be found in the current SmPC.

4.0 Rationale

Humira is approved in the US for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Humira can be used alone or in combination with methotrexate (MTX).

In the EU, Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients 2 years of age and older who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs

(DMARDs). Humira can be given as monotherapy in case of intolerance to methotrexate or when continued treatment with methotrexate is inappropriate.

This protocol describes a post-marketing observational registry that will evaluate the long-term safety and effectiveness of Humira as used in routine clinical practice in patients with moderately to severely active polyarticular or polyarticular-course JIA, who are candidates for anti-TNF therapy. This registry is part of a post marketing commitment from AbbVie to the Food and Drug Administration (FDA), and to the European Medicines Agency (EMA).

The participating physicians, with regard to countries and sites, will be representatives of the pediatric rheumatologists who will prescribe Humira to patients with moderately to severely active polyarticular or polyarticular-course JIA in the US, Europe, and Australia. The patients enrolled in this registry correspond to the target population as described in the current approved Humira label for polyarticular JIA in the participating countries.

The data collected in this registry will be complementary to those from the pre-registration study of Humira in moderately to severely active polyarticular or polyarticular-course JIA. The management of the patients in this registry will be reflective of Humira use for moderately to severely active polyarticular or polyarticular-course JIA post-approval in a routine clinical setting. The participating physician is free to determine the appropriate therapy for each patient. Only after this decision has been made, will the patient be offered participation in the registry.

Patients who consent to participate in the registry, will be followed for up to 10 years starting from Day 1 in the registry arm, providing long-term safety data for 10 years and long-term effectiveness data for 5 years. For the patients in the HUMIRA registry arm after having been initially in the MTX registry arm, the 10 year follow-up will restart from Day 1 in the HUMIRA registry arm.

5.0 Registry Objectives

The primary objective of this registry is to evaluate the long-term safety of Humira in patients with moderately to severely active polyarticular or polyarticular-course JIA who are prescribed and treated in accordance with the approved local Humira product label under the conditions of a routine clinical setting. Patients being prescribed and treated with MTX per the approved local product label will be considered a reference group.

The secondary objective of this registry is to evaluate the long-term effectiveness of Humira in patients with moderately to severely active polyarticular or polyarticular-course JIA who are prescribed and treated in accordance with the approved local Humira product label under the conditions of routine clinical setting. In addition, the impact of treatment interruptions on the safety and effectiveness of Humira will be evaluated as well. Patients being prescribed and treated with MTX per the local product label will be considered a reference group.

6.0 Investigational Plan

Patients, who agree to participate in the registry, will be followed for up to 10 years (within a registry arm), including patients who discontinue Humira (monotherapy or combination therapy with MTX) or MTX (without Humira). For patients who switch from the MTX arm to the Humira arm, the 10-year follow-up period will start at the time of enrollment into the Humira arm. This registry will assess the incidence and rate of Humira (monotherapy or combination therapy with MTX) or MTX observational and treatment-emergent SAEs, Adverse Events of Special Interest (AESI) and Pregnancy in patients diagnosed with moderately to severely active polyarticular or polyarticular-course JIA through Year 5. AESI are listed in Section 7.1.4 of this protocol. Starting at Year 6, patients will be followed annually for SAEs, a subset of AESI that includes congestive heart failure (CHF), malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies through Year 10. For polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group

of patients at the time of consent to the registry, SAEs, all AESI, and pregnancy (at the age when a patient can become pregnant) will be collected for the full 10 years.

Patients who have discontinued or will discontinue from the registry (prior to completion of 10 years) will be contacted to determine interest in enrollment into the direct to HCP (Health Care Provider) follow-up process as described in Section 6.2. AESI, hospitalizations, surgeries and death as listed in Section 7.1.3 and Section 7.1.4 will be collected through Year 5 for those patients who choose to participate in the direct to HCP follow-up process. Starting at Year 6, patients will be followed annually for congestive heart failure, malignancies, hospitalizations, surgeries, and death through Year 10. Any other AEs, SAEs, and/or pregnancies should be reported according to normal spontaneous reporting procedures, and they are not subject to the requirements of this protocol. In countries with available local approval at the time of consent, polyarticular JIA patients 2 to < 4 years of age who discontinue for any reason, will be offered the opportunity to participate in the direct to HCP follow-up process and will be followed for AESI, hospitalizations, surgeries, and death annually for the full 10 years.

6.1 Selection of Population

Once a decision has been made between the physician and the patient to use Humira (monotherapy or combination therapy with MTX) or MTX (without Humira) as part of usual care for and in accordance with approved local prescribing information for polyarticular JIA, sites will be encouraged to offer enrollment to all eligible patients. After a decision to prescribe Humira, patients from previous Humira clinical trials (Study M10-444 and Study DE038) will be offered enrollment in the registry. Prior to collecting registry-related information, a parent or legal guardian must sign a parental consent and patient assent/authorization form, or appropriate forms per local requirements for release of information. Physicians should determine the appropriate therapy for each patient without regard to study participation. The participating physician will provide the patient a prescription for Humira (monotherapy or combination therapy with MTX) or MTX (without Humira) along with instructions for appropriate use in patients with moderately to severely polyarticular JIA.

- Patients prescribed Humira rolling over from another AbbVie clinical study will continue in the Humira arm.
- New patients may be enrolled in one of two arms, the Humira arm or the MTX arm, depending on the treatment decision made by the physician prior to enrollment.
    - Patients in the Humira arm may be treated with Humira alone or in combination with MTX.
    - Patients in the MTX arm may be treated with MTX alone or in combination with other DMARDs, but not with anti-TNFs or other biologic therapies.
- Patients who are non-responders, intolerant to MTX treatment arm or are in need of combination treatment with Humira therapy are eligible to switch to the Humira treatment arm up until enrollment of the last patient into the registry (i.e., until enrollment in the Humira treatment arm is complete).
    - In these cases patients will be required to discontinue from the MTX arm and consent as a new patient in the Humira arm once any Adverse Events of Special Interest and SAEs have been resolved or the AbbVie Study Designated Physician should be contacted to assess the eligibility of a patient to enroll in the Humira treatment arm if an AE is ongoing and eligibility criteria are met.
    - The 10-year follow-up time for these patients begins when these patients start the Humira arm and not the date they started the registry within the MTX arm.
- After the registry enrollment period is closed to the Humira arm, patients wishing to switch to Humira will be discontinued from the MTX treatment arm; however, the patient will be encouraged to remain in the registry and efforts will be made to follow these patients through Year 10 to gather safety data.

6.1.1 Inclusion Criteria

The decision to prescribe either Humira or MTX must be made prior to the decision to enroll a patient in the registry. A patient will be eligible for participation if he/she meets the following criteria:

1. For a patient enrolling into the Humira arm; a pediatric patient diagnosed at any time with moderately to severely active polyarticular or polyarticular-course JIA (defined as arthritis affecting ≥ 5 joints at the time of diagnosis of polyarticular or polyarticular-course JIA) who has been prescribed Humira therapy according to the locally approved Humira product labeling and meets one of the following criteria:
    a. Enrolled patients are 4 to17 years of age as per approved Humira product label with the addition of polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry.
    b. Newly initiated (within 24 months of registry entry) on Humira therapy and has received continuous (no more than 70 consecutive days off drug) Humira therapy, and the physician can provide available source documentation of SAEs, AEs of Special Interest, and dosing information since initiation of therapy;
    c. Or is entering after participation (within 24 months of registry entry or, if longer, continuously treated at the same site) in an AbbVie Humira sponsored study, regardless of age or the number of joints with symptoms of polyarticular JIA, and has received continuous (no more than 70 consecutive days off drug) Humira therapy and the physician can provide available source documentation of SAEs, AEs of Special Interest, and dosing information since initiation of therapy.
2. For a patient enrolling into the MTX arm; a pediatric patient diagnosed at any time with moderately to severely active polyarticular or polyarticular-course JIA (defined as arthritis affecting ≥ 5 joints at the time of diagnosis of polyarticular or

polyarticular-course JIA) who is prescribed MTX therapy alone or in combination with other DMARDs according to the local product labeling (initiated treatment within 24 months of registry entry) and has received continuous therapy and the physician can provide available source documentation of SAEs, AEs of Special Interest, and dosing information since initiation of therapy.

3. Patients who were treated in the MTX arm of this registry and prematurely discontinued from the MTX arm due to being a non-responder, or became intolerant of MTX treatment or are in need of combination treatment with Humira therapy may be eligible to enroll into the Humira treatment arm if all ongoing AEs/SAEs have been resolved, and they meet inclusion criteria and can enroll during the registry enrollment period. In case of ongoing AEs/SAEs at the time of the treatment arm switch, the AbbVie Study Designated Physician should be contacted to assess the eligibility of patient to roll into Humira treatment arm.
4. Parent or guardian has voluntarily signed and dated an informed consent/patient authorization form, approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) if applicable according to local law, after the nature of the registry has been explained and the patient's parent or legal guardian has had the opportunity to ask questions. Pediatric patients will be included in all discussions as per applicable local regulations in order to obtain verbal or written assent.

6.1.2 Exclusion Criteria

1. Patients should not be enrolled into the Humira or MTX arm if they cannot be prescribed and treated in accordance with the approved local Humira and/or with the local MTX product label.
2. Patients should not be enrolled into the Humira or MTX arm if they require ongoing treatment with Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), Enbrel® (etanercept), Remicade® (infliximab) or any other approved biologic agents or investigational agents.

3. Patients should not be enrolled into the MTX arm if they have had prior treatment with any investigational agent or anti-rheumatic biologic therapy such as, but not limited to, Orencia® (abatacept), Enbrel® (etanercept), Remicade® (inflixumab), Rituxan® (rituximab), or Actemra® (tocilizumab).

6.2 Patient Follow-up Criteria – HCP Process

Patients who discontinue full registry participation prior to completing the registry 10 years of follow-up will be offered to participate in the direct to HCP (Health Care Provider) follow-up process, as allowed by applicable local regulations. In order to participate in the direct to HCP follow-up process, the parent or guardian of the patient must sign and date the consent/patient authorization form. Pediatric patients will be included in all discussions as per applicable local regulations in order to obtain verbal or written assent. Patients participating in the HCP follow-up process may not switch registry treatment arms during the HCP follow-up process. To switch to the Humira arm (add on or switch to Humira), an MTX patient following the direct to HCP follow-up process must re-consent at a registry investigative site. The treatment arm at the time of patient authorization will be noted. All data collected post authorization will be included in analysis of the treatment arm indicated at the time of patient authorization, or until the date the patient re-consents in the registry.

6.3 Number of Patients to be Enrolled

This is a multicenter, non-interventional, observational registry of patients' diagnosed at any time with moderately to severely active polyarticular or polyarticular-course JIA, (defined as arthritis affecting ≥ 5 joints at the time of diagnosis of polyarticular or polyarticular-course JIA), prescribed and treated in a routine clinical setting either with Humira or MTX. Approximately 800 patients will be enrolled in the United States, EU countries, and Australia. Approximately 500 patients will receive Humira (alone or in combination with MTX) and 300 patients will receive MTX without Humira.

6.4 Physician Selection Criteria

It is expected that approximately 120 physicians from the United States, European countries, and Australia will participate in this registry. Approximately 40 to 45 physicians will be included based on participation in prior AbbVie Humira sponsored clinical JIA studies.

6.5 Registry Duration

The planned follow-up observation period is 10 years from enrollment into one of the treatment arms. The follow-up period for patients that switch from the MTX arm to the Humira arm will begin when they enroll into the Humira arm, in which case participation would be longer (i.e., up to 10 years from the time of the switch).

A patient may withdraw from the registry at any time without prejudice. If the physician decides it is in the best interest of the patient to discontinue Humira or MTX for any reason, treatment should be stopped. Physicians are encouraged to keep patients in the registry for a full 10-year observation period irrespective of future treatment decisions so important and complete safety and effectiveness information can be obtained. If the patient is not seen at a visit, efforts, i.e., phone, fax, letter, will be made to gather safety data through Year 10.

Patients in the MTX arm who are prescribed Humira treatment must be re-consented before enrolling in the Humira arm during the time that the enrollment period is open (i.e., until enrollment in the Humira treatment arm is complete).

If a patient withdraws or is withdrawn from the registry, this should be noted, along with the reason for withdrawal on the electronic study completion page. At the time of withdrawal from the registry, an assessment of the patient's current medical condition will be completed.

Patients who discontinue from the registry or transition to another HCP will be offered to participate in the direct to HCP follow-up process by their registry physician, as allowed

by applicable local regulations. If the patient (or Parent/Guardian for pediatric patients) agrees, a consent/assent and/or patient authorization for use/disclosure for data (as applicable) will be obtained.

Effectiveness measures will not be collected from patients participating in the direct to HCP process.

6.6 Registry Conduct

Physicians will be provided with a registry kit that includes a protocol, parental informed consent and patient assent forms, and information material to enable access to electronic Case Report Forms (eCRF), including Serious Adverse Event (SAE) Report Forms, and specially designed eCRFs to collect assessment data and AEs of Special Interest (AESI). When applicable, information about the effectiveness of Humira therapy will be provided by the patients and their physician. Effectiveness of therapy provided by the patient will be collected with paper patient questionnaires and visual analogue scales called patient reported outcomes (PROs) for selfadministered assessments, if part of routine clinical care. Physicians will determine the appropriate therapy for each patient in accordance with the locally approved label. The decision to prescribe Humira (monotherapy or combination therapy with MTX) or MTX (without Humira) to the patients should be made separately from the decision to enroll them into the registry.

The physician will follow the patient during regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines.

At the enrollment (baseline) visit, the Investigator will complete the Enrollment eCRFs by obtaining and recording all of the available required information. AEs of Special Interest (Section 7.1.3) in addition to hospitalizations and surgeries meeting SAE criteria (Section 7.1.4) that occurred prior to the enrollment (baseline) visit will be collected on a specially designed questionnaire for entry into EDC.

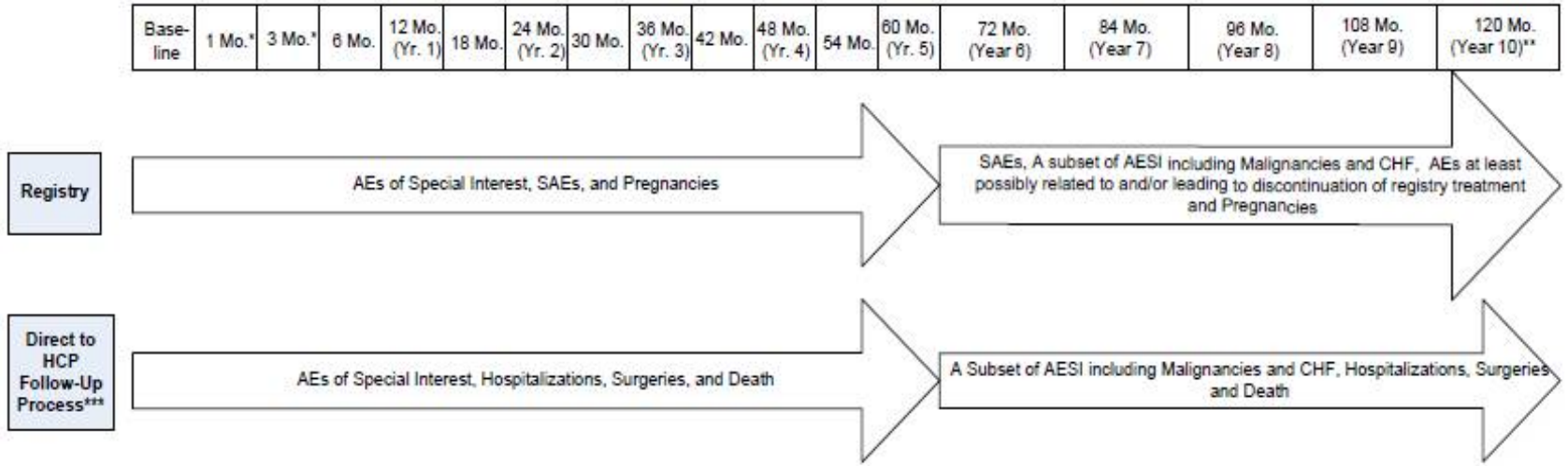
At subsequent visits corresponding to the intervals in the registry activities (Table 1), the Investigator will complete the appropriate eCRF by obtaining and recording all available

information. Since this is an observational registry conforming to usual clinical practice, data will be collected from patient visits that most closely correspond to the protocol intervals in Table 1. Months 1 and 3 (not required for patients who participated previously in an AbbVie sponsored Humira study), and Month 6 followed by routine office visits every 6 months through Year 5. For example, if a patient visits the investigator at Month 5, this is close to the protocol-defined 6-month visit, so data can be collected for this visit. If the same patient unexpectedly returns for a visit the investigator's site at a date closer to the 6 month visit, no further effectiveness data needs to be collected since the data was previously collected. Safety data that meets the criteria for collection should be collected regardless of protocol-defined registry visits.

For collection of Safety data, see Figure 1 and Figure 2.

Figure 1. Registry Schematic for Polyarticular JIA Patients 4 to 17 Years of Age

With HUMIRA®, eow or Methotrexate (as directed)



eow = every other week

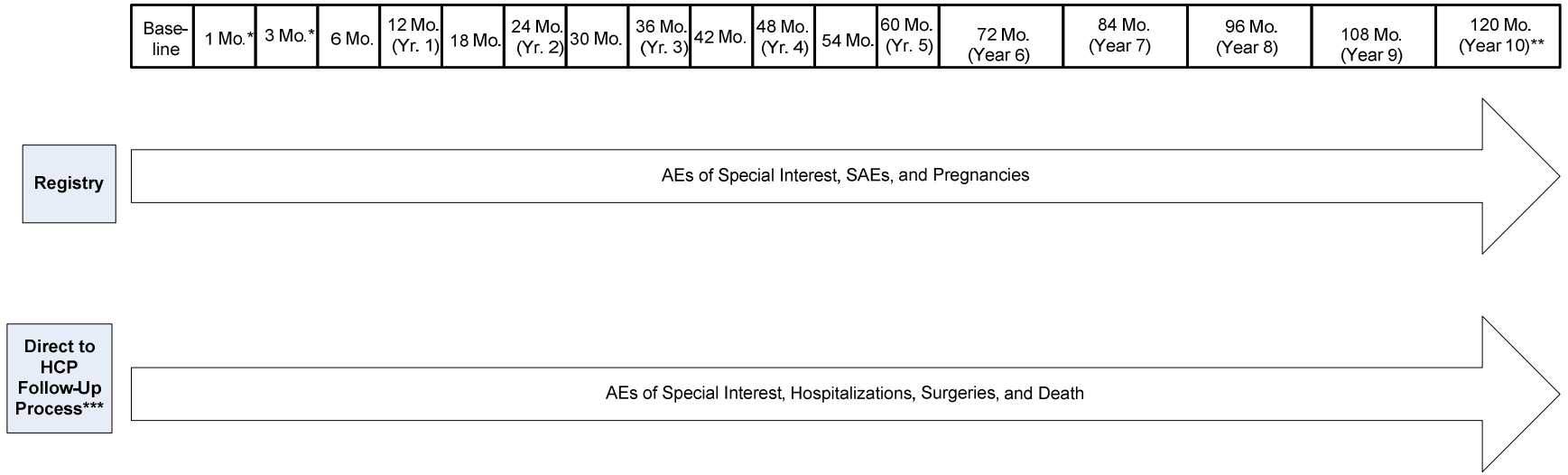
* For patients not rolling over from Study DE038 or Study M10-444.

** Participation in the registry may be longer if patient switches from MTX arm to Humira arm.

*** The Direct to HCP Follow-up Process will collect events annually.

Figure 2. Registry Schematic for Polyarticular JIA Patients 2 to < 4 Years of Age in Countries with Available Local Approval for this Group of Patients at the Time of Consent to the Registry

With Humira, eow or Methotrexate (as directed)



eow = every other week

* For patients not rolling over from Study DE038 or Study M10-444.

** Participation in the registry may be longer if patient switches from MTX arm to HUMIRA arm.

*** The Direct to HCP Follow-up Process will collect events annually.

The physician will then follow the patient during regular office visits at intervals as information about medications taken for polyarticular JIA will be recorded on the CRF at enrollment and at visits closest to the time points in Table 1. While the physician may deem it appropriate and necessary to have the patient return for additional visits during the observation period, data will be collected via Case Report Forms (CRFs) only at the intervals that most closely correspond to those described in Table 1. However, information related to safety should be captured at any time using the appropriate eCRFs.

Physicians should treat their patients as they would in their routine clinical practice. At any time, patients and physicians may choose to interrupt Humira (monotherapy or combination therapy with MTX) or MTX (monotherapy without Humira) therapy for any reason. Patients that intermittently stop treatment (Section 10.1) should continue to be monitored during and after their treatment interruption for safety (SAEs and AEs of Special Interest) and effectiveness. These patients will be asked for changes in their polyarticular JIA medications, concomitant medication and medical history at their baseline visit and at their regularly scheduled visits..

Patients that switch from the MTX arm to the Humira arm will be followed as patients in the Humira arm.

If treatment with Humira (monotherapy or combination therapy with MTX) and/or MTX (without Humira) is permanently discontinued for any reason, patients will be encouraged to remain in the registry. The reason for discontinuation should be documented on the eCRF.

Office visits are optional for patients that discontinue treatment, if the patient is not seen at a visit; both active and passive methods will be used to maintain contact. During enrollment, the patient will be asked by the investigator to provide contact information in accordance with local regulations. All patients who are unreachable after 3 consecutive documented attempts to contact the patient via phone, email, or certified letter, will be considered lost to follow-up.

Sites will be asked to check e.g., National Death Index and national/regional cancer registries and vital registries in other countries in accordance with local regulations where accessible. The site will be asked to perform the vital statistic's matching process approximately annually beginning in the second year of the registry, or as soon as data from the NDI and other registries are available to cover the time period of enrollment. Where allowed per local regulations, the sponsor representative may also be requested to perform the vital statistic's matching process.

All Humira and MTX doses will be given using the respective commercially available drug per prescription and physician's recommendation.

The procedures to be conducted in the registry are outlined in Table 1.

Table 1. Registry Activities

Procedure	Enrollment Visit (BL)	Month[a] 1[c], 3[c], 6, 12[b], 18, 24[b], 30, 36[b], 42, 48[b], 54, 60[b]	Month 72, 84, 96, 108, 120	At Time of Reported Event
Informed Consent/Patient Authorization[d]	√			
Demographics, including Biological Parent Height)	√			
Medical/Surgical Hx (including JIA Medical/ Surgical Hx and tobacco and alcohol use)	√			
Pre-Registry Exposure to Humira[e]	√			
Vital Signs and Growth Assessment/	√	√		
Tanner Maturation Staging[b]	√	√		
Safety Data Collection (AEs of Special Interest/SAEs)[f]	√	√	√	√
Previous JIA therapies	√			
Concomitant JIA therapies	√	√		√
Concomitant medications at time of reported SAE or AE of interest				√
Laboratory Assessments[g]	√	√		√
Physician Global Assessment (VAS)	√	√		
Parent's Global Assessment (VAS)	√	√		
DICHAQ	√	√		
CHQ-PF50	√	√		
Joint Assessment	√	√		
Inactive/Active Disease Status	√	√		
Eye Disease (Uveitis) Assessment	√	√		√
Humira Treatment and Dosing Changes	√	√	√	√
MTX Registry Treatment and Dosing Changes	√	√	√	√
Case Report Form Completion	√	√	√	√
70-Day Follow Up Call[h]		√	√	

a. Data collection at regular visits that are closest to time points described. For patients participating in the HCP questionnaire process, follow-up is annually.

b. Tanner Maturation Staging should be completed annually through Year 5, as applicable.

c. Patients that have not rolled over from AbbVie Study DE038 or Study M10-444 will have additional visits at Month 1 and 3.

d. Patients that switch from the MTX arm to the Humira arm must be re-consented.

e. Medical assessments from the first dose of commercial Humira will be collected to enter into this registry.

Table 1. Registry Activities (Continued)

f. AESI, SAEs and pregnancies will be collected from Year 1 through Year 5. From Year 6 through Year 10 SAEs, a subset of AESI that includes congestive heart failure (CHF), malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment and pregnancies will be collected. For patients that participate in the direct to HCP follow-up process AESI, hospitalizations, surgeries, and death will be collected annually from Year 1 through Year 5 and malignancies, CHF, hospitalizations, surgeries and death will be collected annually from Year 6 to Year 10. For polyarticular JIA patients from 2 to < 4 years of age while in the registry AESI, SAEs and pregnancies will be collected through Year 10 and those who participate in the direct to HCP follow-up process will have AESI, hospitalizations, surgeries and death collected annually through Year 10.

g. Provide local lab values including but not limited to ESR, CRP, anti-nuclear antibody (ANA), and any labs related to SAE's or AEs of Special Interest (i.e., CPK, presence of lupus anticoagulants or anticardiolin antibodies). The assessments will be collected at baseline and afterwards only when part of physician's site routine care.

h. Patients who develop an Adverse Event of Special Interest (AESI) or SAE while in the registry will be followed throughout the patient's participation in the registry or direct to HCP follow-up process until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer). Follow-up received on ongoing SAEs and/or AESI post registry conclusion should be reported using standard Post Marketing Reporting.

The procedures outlined in Table 1 are discussed in detail in this section, the exception of the collection of AE information, which is discussed in Section 7.1.1 and Informed consent/patient authorization which is discussed in Section 8.0. For patients participating in the HCP follow-up process, follow-up is done annually as defined in the protocol and only AESI, surgeries, hospitalizations, and death are collected through completion of Year 5. Starting from Year 6 from initial registry enrollment, patients participating in the HCP questionnaire process will be followed annually for congestive heart failure, malignancies, hospitalizations, surgeries, and death through Year 10 (Figure 1). For polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry and participating in the HCP follow-up process will have AESI, hospitalizations, surgeries and deaths collected for the full 10 years as defined by the protocol (Figure 2). Any other AEs, SAEs, and/or pregnancies should be reported according to normal spontaneous reporting procedures, and they are not subject to the requirements of this protocol.

6.6.1 Demographics

The physician will obtain patient demographic information at the enrollment visit and record it on the Baseline eCRF. The demographic information will include date of birth,

sex, race, and ethnicity (according to local regulations). Demographic data will not be captured for patients rolling over from a previous Humira (adalimumab) study as this information has already been collected. Only the patient number from the previous clinical study will be recorded in the eCRF required.

Parental heights will be requested from the biological parents, upon consent, which will be used in the analysis of the patient's growth assessment.

6.6.2 Medical History

A complete non-polyarticular JIA related medical and surgical history as well as a history of tobacco and alcohol use will be obtained from each patient at the enrollment visit. A list of each patient's specific polyarticular JIA related medical and surgical history should be recorded in addition to the disease category, activity and the disease onset. For patients rolling over from a previous Humira clinical study, any ongoing AEs and SAEs as well as medical conditions requiring concomitant medication treatment will be captured as medical history items. The onset type of the disease will be recorded, if available, while a detailed medical history will not be required, unless information was omitted upon entry to the prior AbbVie Humira clinical study.

Patients will be asked to provide retrospective SAEs, Adverse Events of Special Interest, and exposure to MTX and/or Humira data, if available upon consent, from the first dose of MTX and/or commercial Humira to entry into this registry.

6.6.3 Vitals, Growth Assessments and Tanner Staging

Vitals including blood pressure, pulse, temperature, will be recorded at Baseline and at each visit through Year 5. Growth assessments, including height and weight, will be recorded at Baseline and at each visit through Year 5 and Tanner Maturation Staging (Appendix H) will be recorded at Baseline and every 12 months thereafter through Year 5. Biological parent's height will also be collected at the Baseline Visit if consent was obtained.

6.6.4 Prior and Concomitant Medications

Any DMARD and biologic treatments previously administered and the reason for discontinuation (i.e., AE, lack of effectiveness, intolerance or other) will be recorded. Information on the highest maintained dose, date of last administration, length of time on the medication and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving at the time of screening, and/or receives during the registry, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency on the appropriate eCRF.

Intra-articular and/or soft-tissue corticosteroid injections must be captured, however the joint that is injected should be considered non-evaluable for 3 months thereafter.

Kineret® (anakinra), Orencia® (abatacept), Rituxan® (rituximab), Enbrel® (etanercept), Remicade® (infliximab) or other approved biologic agents are not to be given concurrently while participating in the registry as per the labeling for MTX and Humira.

Patients should not be enrolled into the MTX arm if they have had prior treatment with any investigational agents or anti-rheumatic biologic therapies such as, but not limited to, Orencia® (abatacept), Enbrel® (etanercept), Remicade® (inflixumab), Rituxan® (rituximab), or Actemra® (tocilizumab). Patients in the MTX arm may be prescribed and treated with MTX alone, or in combination with other DMARDs but not with anti-TNFs or other biologic therapies at the time of enrollment.

Patients in MTX arm that require treatment with the biologic/anti-TNF will be excluded from the MTX treatment arm but may continue within the registry. After the Humira treatment arm enrollment is complete, if a patient in MTX treatment arm begins Humira therapy, Humira will be considered a concomitant medication.

Except for live vaccines, patients may still receive vaccines while on Humira. It is recommended that children with JIA be brought up to date with all immunizations prior to starting Humira.

The AbbVie Study Designated Physician identified in Section 7.1.8 should be contacted if there are any questions regarding concomitant or prior therapies.

In addition for patient's age ≤ 30 with a reported malignancy event, prior exposure to, or current use of antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the registry will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

During registry participation, patients should not be enrolled into any interventional clinical trials.

6.6.5 Safety Data Collection

The following safety information will be collected from the time the parental consent and patient assent forms are signed: AEs of Special Interest and SAEs. The Physician will assess and record the AE in detail including the date of onset, description, severity, time course, duration and outcome, relationship of the AE to treatment, an event diagnosis, if known, and any action(s) taken. For SAEs considered "possibly related," "probably not related" and "not related" to the registry treatment, the Physician will provide the alternative etiology of the event. Information about medications taken to treat the SAE or the Adverse Event of Special Interest will be collected.

During the first 5 years of the registry, all available patient data, including SAEs, AESI as defined by the protocol and pregnancies will be collected at each doctor's visit. However, SAEs, AESI and pregnancy information can be collected at any time during the registry, not only at each doctor's visit. During Years 6 through 10 of the registry, patient data will be collected annually, including SAEs, a subset of AESI that includes congestive heart failure, malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies (Figure 1). Polyarticular JIA patients 2 to < 4 years of age, in countries with available local approval for this group of patients at the time of consent to the registry, will have SAEs, AESI, and pregnancy (potentially at the age when patient can become pregnant) collected for the full 10 years as defined by the protocol (Figure 2). Patients who develop an SAE or Adverse Events of Special Interest (AESI) while in the registry will be followed throughout the patient's participation in the registry until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

For patients participating in the HCP process, safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire to be used through Year 5 focuses on the collection of Adverse Events of Special Interest (AESI), hospitalizations, surgeries, and death. The questionnaire to be used for Years 6 through 10 focuses on collection of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group, will have AESI, hospitalizations, surgeries and death collected for the full 10 years as defined by the protocol (Figure 2). The questionnaire may be completed by the registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician).

All patients who participate in or discontinue from the registry during the first 5 years will be followed for SAEs and AEs of Special Interest until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the registry during Years 6

through 10, will be followed for all SAEs, CHF and malignancies until satisfactory conclusion or for 70 days after last dose of registry drug (whichever is longer) to evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up through Year 5 will be followed for AESI, hospitalizations, surgeries and death until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up during Registry Year 6 through Year 10 will be followed for malignancies, CHF, hospitalizations, surgeries, and death until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 1).

All polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry who participate in or discontinue from the Registry up through Year 10 will be followed for AESI and SAEs until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All polyarticular JIA patients 2 to < 4 years of age who participate in or discontinue from the direct to HCP follow-up process up through Registry Year 10 will be followed for AESI, hospitalizations, surgeries and death until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 2).

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.3.

6.6.6 Physician Global Assessment and Patient Reported Outcome Measurements

Information about the effectiveness of Humira or MTX therapy will be provided by the patient's parent or guardian and their physician. Patients and/or parents will complete the questions directly on the paper case report form (CRF) and the CRF pages will be

considered source documents. Effectiveness of therapy provided by the patient will be collected with clinical assessments beginning with the enrollment visit, at regularly scheduled visits which are closest to Months 1 and 3 (if applicable) and 6 and then every 6 months through Year 5. The following clinical assessments will be used: physical function of the Disability Index of Childhood Health Assessment Questionnaire (DICHAQ), and Parent's Global Assessment of Patient's Disease Activity (VAS) and Parent's Assessment of patient's pain (VAS). Effectiveness of therapy provided by the physician will be collected through the Physician's Global Assessment of Disease Activity (VAS).

The Child Health Questionnaire (CHQ-PF50) in Appendix G will be used to assess quality of life for children with polyarticular JIA through Year 5.

Physician Global Assessment and Patient Reported Outcome Measurements will not be collected after the completion of Year 5.

6.6.7 Joint Assessment

A thirty-nine joint assessment (Appendix D) will be recorded starting at the enrollment visit and at each registry visit thereafter through Year 5 to assess the number of active joints.

6.6.8 Laboratory Assessments

There are no required laboratory tests for this registry. Laboratory tests, such as chemistry, hematology, and erythrocyte sedimentation rate (ESR), will be collected when part of the physician's site routine care. However to assess the PedACR score, it is recommended that CRP and/or ESR be provided where available. If available as part of routine care, anti-nuclear antibody (ANA) and past or current genetic testing results HLA-B27 will be collected. There is no central laboratory for this registry; therefore all lab assessments will be conducted by a local laboratory at the physician's discretion and collected where available.

6.6.9 Inactive Disease Assessment

The inactive disease assessment will be recorded starting at the enrollment visit and at each registry visit thereafter through Year 5. A patient has inactive disease if he/she meets the following:

- No active arthritis
- No fever
- No rash
- No serositis
- No splenomegaly
- No generalized lymphadenopathy attributable to JIA
- No active uveitis in connection with JIA
- Normal ESR or CRP level only when part of the physician's site routine care
- Physician's global assessment of disease activity indicating clinical disease quiescence.

6.6.10 Assessment of JIA Associated Uveitis

Data will also be collected for patients with uveitis in connection with their JIA (pre-registry onset and new onset of JIA associated uveitis during the registry participation) to determine how strongly it affects their ability to function normally through Year 5, as applicable.

For patients with JIA associated uveitis it is requested that the treating Rheumatologist obtains the assessment results from the patient's Ophthalmologist according to the local clinical practice for the following:

- Uveitis manifestation
- Uveitis localization
- Summarizing evaluation of uveitis by eye as:
  - No irritation

- Less inflammation
- No change in uveitis
- More inflammation

compared to uveitis at prior registry visit (starting with registry visit after Baseline as applicable)

- New/additional complications in uveitis since last registry visit (starting with registry visit after Baseline as applicable)
- Actual Visual Acuity by eye
- Anterior Chamber Cells
- Vitreous Haze

6.6.11 Humira and Methotrexate Treatment and Dosing Changes

Prior to enrolling a patient into the registry, the participating Physician will provide the patient a prescription for Humira or MTX along with instructions for appropriate use. At each registry visit, the Physician will collect the start and stop dates (if applicable), any dose interruptions and reason for the dose interruption that may have occurred since the last registry visit. The dose, dates of administration, any dose interruptions or changes, and the reason for the interruption will be captured in the source documents and eCRFs. Humira and MTX registry treatments and dosing changes will be collected through registry Year 10.

6.6.12 Product Supply

AbbVie will not provide any medication or therapy for this registry. Patients will receive commercial product as prescribed by their treating physician.

6.7 Effectiveness and Safety Assessments/Variables

This is a long-term observational registry with the objective of documenting safety and effectiveness of Humira, using MTX as a reference, in routine clinical practice.

6.7.1 Effectiveness Variables

Information to evaluate the effectiveness of Humira or MTX therapy will be collected from patients and their physicians if part of routine clinical assessment. In the event Humira therapy is interrupted, effectiveness variables will be collected during the interruption.

The effectiveness of therapy evaluation provided by the patient or parent will be collected with clinical assessments as discussed in Section 6.6.6. The following clinical assessments will be used:

- Parent's Assessment of Patient's Pain (VAS)
- Parent's Global Assessment of Patient's Disease Activity (VAS)
- Physical function of the DICHAQ
- Child's Quality of Life CHQ-PF50

Effectiveness of therapy provided by the physician will be collected through the Physician's Global Assessments, if part of routine clinical assessment. The following assessments will be collected:

- Physician's Global Assessment of Disease Activity (VAS) (Appendix F)
- Joint pain and swelling
- Number of active joints
- Number of joints with limitation of passive motion (LOM)
- Number of joints with pain on passive motion (POM)
- CRP and/or ESR level only when part of the physician's site routine care

Patients may also be evaluated for inactive disease. The criterion for inactive disease includes the following:[17]

- No active arthritis
- No fever

- No rash
- No serositis
- No splenomegaly
- No generalized lymphadenopathy attributable to JIA
- No active uveitis in connection with JIA
- Normal ESR and/or CRP level only when part of the physician's routine care
- Physician's global assessment of disease activity indicating clinical disease quiescence.

6.7.2 Safety Variables

The physician will be asked to document SAEs and Adverse Events of Special Interest (AESI) on eCRFs (Section 7.0).

SAEs and Adverse Events of Special Interest (AESI) will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent/patient authorization) throughout the registry or Direct to HCP follow-up process until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest (AESI) will be collected throughout the interruption. If a patient switches from MTX to Humira treatment, SAEs and AEs of Special Interest will continue to be collected under the Humira arm. If treatment with Humira or MTX is permanently discontinued for any reason, patients will be discontinued from treatment and the reason for discontinuation will be recorded on the Study Drug Completion eCRF. Patients that discontinue treatment will be encouraged to remain in the registry and will be followed for safety and effectiveness through Year 5 and SAEs and AESI will be followed until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer), and starting at Year 6, patients will be followed annually for the subset of AESI which include congestive heart failure and malignancies and SAEs through Year 10 of the registry until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). For polyarticular

JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry the AESI and SAEs will be collected for the full 10 years as defined by the protocol (Figure 2) and will be followed up until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). Patients that discontinue from the Registry (before 10 years) will be offered to participate in the direct to HCP process as allowed by applicable local regulations. Safety data from these patients will be collected by completion of a simplified HCP questionnaire on an annual basis. The questionnaire focuses on the collection of Adverse Events of Special Interest, hospitalizations, surgeries, death and polyarticular JIA related medication use through Year 5 and malignancies, CHF, hospitalizations, surgeries and death from Year 6 through Year 10 (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry and participating in the HCP follow-up process will have AESI, hospitalizations, surgeries, death and polyarticular JIA related medication use collected for the full 10 years (Figure 2).

SAEs, Adverse Events of Special Interest (AESI), and pregnancies will be collected on their respective eCRFs (refer to Section 7.0 and Section 7.1.9 for details).

6.8 Removal of Patients from Therapy or Assessment

6.8.1 Discontinuation of Individual Patients

A patient may withdraw from the registry at any time without prejudice due to withdrawal of consent, lost to follow-up as defined below, or death.

If the Physician, for any reason, decides it is in the best interest of the patient to discontinue Humira or MTX, treatment should be stopped. A patient that discontinues Humira or MTX treatment will be encouraged to remain in the registry. Efforts will be made to follow all patients through Year 5 of the registry for safety and effectiveness and from Year 6 through Year 10 congestive heart failure, malignancies, pregnancies and SAEs. For polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry the AESI,

SAEs and pregnancy (potentially during the study at the age when patient can become pregnant) will be collected for the full 10 years as defined by the protocol (Figure 2). The following reasons, but not limited to, for treatment discontinuation should be noted on the eCRFs.

- Clinically significant abnormal laboratory results or AEs, which prevent continuation of Humira (monotherapy or combination therapy with MTX) and/or MTX (monotherapy without Humira) as determined by the Physician.
- The physician believes it is in the best interest of the patient.
- The parent, legal guardian, or patient requests withdrawal from the registry.
- The patient is lost to follow-up, i.e., does not provide data for ≥ 1 year and does not respond to notifications from the site.
- The patient receives a concomitant biologic anti-rheumatic therapy other than Humira.
- The patient is diagnosed with a malignancy except for localized non-melanoma skin cancer. Discontinuation for carcinoma-in-situ is at the discretion of the Physician.
- Patients who interrupt their Humira or MTX therapy and do not restart within 1 year.
- Lack of effectiveness.

Patients who have discontinued from the registry prior to Year 10 will be contacted to determine interest in participation in direct to HCP process that includes the HCP's completion of a simplified HCP questionnaire on an annual basis.

7.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The Sponsor's product in this registry contains both:

- Biologic compound(s) and
- Device component(s) (pre-filled syringe, pen).

Complaints associated with any component of the Sponsor's product must be reported to the Sponsor. For adverse events, please refer to Sections 7.1 through 7.1.8. For product complaints, please refer to Section 7.2.

7.1 Medical Complaints

7.1.1 Adverse Events

Adverse Events/Adverse Events of Special Interest Reporting:

The Physician will monitor each patient from the time the applicable registry-specific parental informed consent/patient assent form (authorization form) is signed throughout the Registry participation for all Adverse Events as described in Section 6.6.5 (Safety Data Collection).

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.3.

The Physician will assess and record the AE in detail including the date of onset, signs/symptoms, severity, time course, duration and outcome, relationship of the AE to treatment, an event diagnosis, if known, and any action(s) taken. For SAEs considered "possibly related," "probably not related" "and not related" to the registry treatment, the Physician will provide another cause of the event. For AEs to be considered sporadic, the events must be of similar nature and severity. SAEs or Adverse Events of Special Interest, whether in response to a query, observed by site personnel, or reported

spontaneously by the patient will be recorded. Information about medications taken for the SAE or the Adverse Event Special Interest will be collected.

All events reported throughout the patient's participation in the registry will be followed until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

7.1.2 Adverse Event Definition

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in permanent or temporary discontinuation of treatment with Humira or MTX, necessitate therapeutic medical intervention and/or if the Physician considers them to be AEs.

An elective surgery/procedure scheduled to occur during the registry will not be considered a SAE if the surgery/procedure is being performed for a pre existing condition and the surgery/procedure has been pre planned prior to entry to the registry. However, if the pre existing condition deteriorates unexpectedly during the registry (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

7.1.3 Adverse Events of Special Interest

The Physician will monitor each patient for clinical and laboratory evidence for pre-defined Adverse Events of Special Interest at the Baseline visit and on a routine basis through Year 10 of the registry as mentioned in Section 6.5 Registry Duration.

AEs of Special Interest for this registry include:

- Serious and nonserious opportunistic infections including the following bacterial, fungal, viral, and parasitic infections: Aspergillus, Blastomyces, Candida, Coccidiodes, Cryptococcus, Cytomegalovirus, Histoplasma, Listeria, Nocardia, Paracoccidiodes, Pneumocystis, Toxoplasma, Tuberculosis, Herpes, Bacillary angiomatosis, Mucormycosis, Progressive Vaccinia, Zygomycosis, BK virus, and JC virus.
- Hypersensitivity reaction to Humira injection
- Lymphoma
- Hepatosplenic T-cell lymphoma
- Non-melanoma skin cancer (NMSC)
- Leukemia
- Other malignancies (except lymphoma and NMSC)
- Immune reactions including lupus, lupus-like reactions, and severe allergic reactions
- CNS demyelinating disorders (including MS and Guillain-Barré syndrome and optic neuritis)
- Hematologic events that are serious or lead to permanent discontinuation of treatment (e.g., aplastic anemia, granulocytopenia, granulocytes maturation Arrest, Leucopenia, Neutropenia, Pancytopenia, and Thrombocytopenia)
- Hepatic events that are serious or lead to permanent discontinuation of treatment (e.g., persistent liver function test abnormalities, acute liver failure, and other serious hepatic events)
- Vasculitis
- Diverticulitis

- Intestinal perforation
- Congestive heart failure (CHF)
- Severe CPK elevations (defined as CTC grade 3 and above) and associated clinical syndromes
- New onset seizure disorders defined as any new epilepsy disorder diagnosed within the timeframe of the registry
- Antiphospholipid syndrome and associated autoantibodies
- New onset or worsening of Psoriasis
- All events leading to premature discontinuation of treatment (Note: limited to only Adverse Events of Special Interest [listed above] leading to premature discontinuation for patients participating in the direct to HCP process)
- All events that are probably or possibly related to treatment (Note: limited to only Adverse Events of Special Interest [listed above] that are probably or possibly related to treatment for patients participating in the direct to HCP process)

Antiphospholipid syndrome is defined as the presence of lupus anticoagulants (LA) or anticardiolipin antibodies (aCL) plus the presence of these antibodies in patients with arterial or venous thrombosis or pregnancy morbidity. At least one laboratory criterion and one clinical criterion must be present. Clinical criteria include objectively confirmed arterial, venous, or small-vessel thrombosis, or pregnancy morbidity consisting of recurrent fetal loss before the 10^{th} week of gestation, 1 or more unexplained fetal death at or beyond the 10th week of gestation, or premature birth due to placental insufficiency, eclampsia, or preeclampsia. Laboratory criteria include medium or high titer Immunoglobulin G (IgG) or Immunoglobulin M (IgM) aCL or the presence of LA on 2 or more occasions at least 6 weeks apart.

Additional follow-up for the occurrence of malignancies and congestive heart failure is required annually for patients completing assessment through 5 years. Occurrence of malignancies and congestive heart failure will be collected for a total of 10 years starting from the registry entry date.

During the course of the registry additional Adverse Events of Special Interest may be identified by AbbVie. Updates to the Adverse Events of Special Interest will be maintained and collected through the eCRF system. Sites will be trained on all updates to the eCRF system.

The Physician will assess and record any additional information on the Adverse Events of Special Interest in detail on the Adverse Events of Special Interest eCRF.

The Physician will assess all reported Adverse Events of Special Interest for seriousness and follow the requirements/timelines for reporting any AEs of Special Interest that fulfills the criteria of an SAE, as defined in Section 7.1.4.

7.1.4 Serious Adverse Events

If an AE meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE. SAEs are required to be reported to AbbVie through Year 10.

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 or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the patient's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results 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 registry patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and 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.
Spontaneous Abortion	Miscarriage experienced by registry patient.
Elective Abortion	Elective abortion performed on registry patient.

An elective surgery/procedure scheduled to occur during the registry will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to registry entry. However, if the pre-existing condition deteriorates unexpectedly during the registry (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

7.1.5 Adverse Event Severity

The Investigator will use the following definitions to rate the severity of each AE:

Mild	The AE is transient and easily tolerated by the patient.
Moderate	The AE causes the patient discomfort and interrupts the patient's usual activities.

Severe	The AE causes considerable interference with the patient's usual activities and may be incapacitating or life-threatening.

7.1.6 Relationship to Pharmaceutical Product

The Investigator will use the following definitions to assess the relationship of the AE to the use of pharmaceutical product:

Probably Related	An AE has a strong temporal relationship to pharmaceutical product or recurs on re-challenge and an Other cause of event is unlikely or significantly less likely.
Possibly Related	An AE has a strong temporal relationship to the pharmaceutical product and an Other cause of event is equally or less likely compared to the potential relationship to pharmaceutical product.
Probably Not Related	An AE has little or no temporal relationship to the pharmaceutical product and/or a more likely Other cause of event exists.
Not Related	An AE is due to an underlying or concurrent illness or effect of another drug and is not related to the pharmaceutical product (e.g., has no temporal relationship to pharmaceutical product or has a much more likely other cause of event).

If an Investigator's opinion of possibly, probably not, or not related to pharmaceutical product is given, an Other cause of event must be provided by the Investigator for the SAE.

7.1.7 Adverse Event Collection Period

Adverse Events of Special Interest will be reported any time after the last dose MTX or Humira if the Physician believes the event is related to MTX or Humira treatment. In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest will be collected throughout the interruption. If treatment with MTX or Humira is permanently discontinued for any reason, the reason will be recorded, and the patient will be

encouraged to remain in the registry. For patients enrolled from the prior polyarticular juvenile idiopathic arthritis (JIA) Humira study, ongoing AEs will be collected within the primary clinical trial and will be captured as part of the patient's medical history in the registry.

During the first 5 years of the registry, all available patient data, including SAEs, AESI as defined by the protocol and pregnancies will be collected at each doctor's visit. However, SAEs, AESI and pregnancies can be collected at any time, not only at each doctor's visit. During Years 6 through 10 of the registry, patient data to be collected annually, including SAEs, a subset of AESI that includes congestive heart failure, malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry will have SAEs, AESI, and pregnancy (potentially at the age when patient can become pregnant) collected for the full 10 years as defined by the protocol (Figure 2). Patients who develop an SAE or Adverse Event of Special Interest (AESI) while in the registry will be followed throughout the patient's participation in the registry until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

For patients participating in the HCP process, safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire to be used through Year 5 focuses on the collection of Adverse Events of Special Interest (AESI), hospitalizations, surgeries, and death. The questionnaire to be used for Years 6 through 10 focuses on collection of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death (Figure 1). In addition, for polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group, Safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire will focus on collection of AESI, hospitalizations, surgeries, and death and will be collected for the full 10 years as defined by the protocol (Figure 2). The questionnaire may be completed by the registry physician

or the patient's current HCP (if the patient is no longer under the care of a registry physician).

The Follow-up received on any ongoing SAEs and/or AESI post registry conclusion should be reported using standard Post Marketing Spontaneous Reporting.

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.3.

7.1.8 Serious Adverse Event Reporting

In the event of a SAE, and additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to registry drug or not, the physician will notify the AbbVie Clinical Pharmacovigilance Team within 24 hours of the physician becoming aware of the event by entering the Serious Adverse Event or nonserious event of malignancy in patients 30 years of age and younger into the electronic data capture (EDC) system. Serious Adverse Events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the EDC system or if the EDC is not operable should be documented on the SAE Non-CRF paper forms and emailed to AbbVie Clinical Pharmacovigilance or faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the Serious Adverse Event.

For SAE concerns, contact the Immunology Safety Team at:

[redacted]

For any subject safety concerns, please contact the Primary Study Designated Physician listed below:

[redacted]

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: [redacted]

7.1.9 Pregnancy

Pregnancy in a registry patient must be reported to AbbVie (see contact details in Section 7.1.8) within 1 working day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected. Pregnancies will be collected from the date of the patient's first dose of registry drug through 150 days following the last dose or the end of the patient's participation in the registry (whichever is longer).

Pregnancy in a registry patient is not considered an AE. However the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

7.2 Product Complaint

7.2.1 Definition

A Product Complaint is any Complaint (see Section 7.0 for the definition) related to the biologic or drug component of the product or to the medical device component.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

7.2.2 Reporting

Product Complaints concerning the product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Product complaints involving a non-Sponsor drug, device or combination product, under study, should be reported to the identified contact or appropriate manufacturer, as necessary per local regulations.

7.3 Data Collection Procedures for Patients Who Participate in the Direct to HCP Process

For patients participating in the direct to HCP process, HCPs will document any Adverse Event of Special Interest, hospitalizations, surgeries, and death as defined in Section 7.1.3 annually via a paper questionnaire or eCRF through the first 5 years of the patient's enrollment date in the registry. HCPs will document any occurrence of hospitalizations, surgeries, death, malignancies, and CHF annually via a questionnaire or eCRF beginning at Year 6 through Year 10. HCPs will document any occurrence of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death

annually via a questionnaire or eCRF beginning at Year 6 through Year 10. For polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry the AESI, hospitalizations, surgeries and death will be collected for the full 10 years as defined by the protocol (Figure 2). The HCP will collect and record the date of onset (where known), and description of the event. The use of other medications used to treat polyarticular JIA, and the start and stop dates for Humira and/or MTX will be collected on an annual basis.

Effectiveness data will not be collected as part of the direct to HCP process.

8.0 Ethics and Quality

The applicable informed consent/patient assent form or patient authorization will be obtained from the parent or legal guardian at the Baseline visit before any registry procedures are undertaken. Additionally, a written informed assent must be obtained from all children ≥ 9 years old or according to the local regulations prior to any registry-related procedures. If a patient becomes of legal age during the course of the registry, that patient will need to be re-consented.

Prior to consenting, the Physician or designee will explain to the parent or legal guardian and to the patient the nature and purpose of the registry and the data to be provided to the sponsor. Upon consent, the parent or legal guardian is allowing the release of patient's information to AbbVie (Sponsor), which can be modified according to local requirements. After the informed consent/patient authorization form is signed, the form will be placed in the patient's medical record and a signed copy should be given to the patient.

Patients that prematurely discontinue from the MTX arm of this registry and meet the requirements for entry in the Humira arm will need to re-consent.

8.1 Quality Assurance

Every registry site will obtain IEC/IRB approval, if applicable (of this registry protocol and related informed consent/patient authorization), prior to initiating the registry at that

site. It shall be the Physician's responsibility to secure such approval prior to further initiating any registry procedures.

The Investigator or his/her representative will explain the nature of the registry to the patient's parent or legal guardian, and answer all questions regarding this registry. Prior to any registry-related screening procedures being performed on the patient, the informed consent/patient authorization form will be reviewed and signed and dated by the patient's parent or legal guardian and the person who administered the informed consent/patient authorization form. Additionally, a written informed assent must be obtained from all children ≥ 9 years old prior to any registry-related procedures or according to age restrictions of the local regulations. If a patient becomes of legal age during the course of the registry, that patient will need to be re-consented.

A copy of the informed consent/patient authorization and informed assent form(s) will be given to the patient and the original will be placed in the patient's medical record. An entry must also be made in the patient's dated source documents to confirm that informed consent/patient authorization was obtained prior to any registry-related procedures and that the patient received a signed and dated copy. A copy of the patient signed informed consent/assent or patient authorization form (as applicable) will be provided to the HCP.

Prior to the site's initiation of the registry, a Physician's meeting will be held with AbbVie personnel, the physicians, and their coordinators, the UBC project manager and the CRAs for the registry. This meeting will include a detailed discussion of the protocol, performance of registry procedures and paper and eCRF completion. In addition to or instead of the Physician's meeting, the personnel at each site may be trained on the registry procedures via web-based training, by a CRA at a registry initiation visit via the telephone or on site and will be given a paper and eCRF completion workbook for reference.

At least one monitoring visit will be performed at each site for the duration of the registry. During the monitoring visit entries on the eCRF are reviewed against source documents to verify accuracy and appropriate completion of the eCRF. The monitoring plan will detail

how sites will be selected for the monitoring visits and what data will be source data verified during the visit. Throughout the registry, UBC and AbbVie (if needed) will periodically follow-up with the sites to ensure that SAEs and Adverse Events of Special Interest are being reported.

All data will be entered in the registry via the eCRF and questionnaires will be completed on paper CRFs. All eCRF information will be imported directly into the electronic data capture system. Paper case report forms are first quality controlled checked and then entered into the electronic data capture system. All other paper questionnaires (e.g., direct to HCP questionnaire) will be reviewed for completion by the site or the CRO (as appropriate) prior to being entered into the database. After entry of the data, computer logic checks will be run to check for inconsistent registry data. Any necessary corrections will be made to the database and documented via addenda, queries, supplemental data clarification form (SDCF) or audit trail. A manual review of selected line listings will also be performed at the end of the registry.

The Investigator should not implement any deviation from the protocol without prior review and agreement by the Sponsor **and** in accordance with the IEC/IRB and local regulations, except when necessary to eliminate an immediate hazard to registry patients. When a deviation from the protocol is deemed necessary for an individual patient, the Investigator must contact their monitor upfront who will contact the Sponsor.

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the patient and/or the registry. Any significant protocol deviations affecting patient eligibility and/or safety must be reviewed and/or approved by the IEC/IRB and regulatory authorities, as applicable, prior to implementation.

9.0 Case Report Forms and Source Documents

All clinical data associated with this registry will be collected and reported electronically (eCRF) via a web address and secure password. Patient questionnaires will be completed

on paper forms and sent to United BioSource Corporation (UBC) Data Management for entry by mail.

At the enrollment visit, the Physician will complete the Enrollment eCRFs by obtaining and recording all available required information, including visit date, demographic data, concomitant diseases and concomitant medications.

At subsequent visits corresponding to the schedule of assessments (Table 1), the Physician will complete the appropriate eCRF by obtaining and recording all available information. Since this is an observational registry conforming to usual clinical practice, data from patient visits that most closely correspond to the recommended schedule of assessment at Months 1 and 3 (if applicable), 6, 12, 18, 24, 30, 36, 42, 48, 54, 60, 72, 84, 96, 108 and 120 will be accepted. Retrospective SAEs and AESI will be captured during the enrollment visit.

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this registry must be recorded on the appropriate source documents. Patient completed questionnaires (DICHAQ, CHQ-PF50); parent's global assessment of patient's disease activity (VAS), parent's assessment of patient's pain (VAS), physician's global assessment of disease activity (VAS) and joint assessments will be documented on a paper Case Report Form, which will be sent to UBC for data entry.

Paper questionnaires or eCRFs will be generated for patients that have discontinued from the Registry and where consent/assent to data release has been obtained for the HCP data collection on an annual basis. Patients will be followed for hospitalizations, surgeries, death, and any Adverse Event of Special Interest as defined in Section 7.1.3 via a paper questionnaire or eCRF through the first 5 years of the patient's enrollment date. HCPs will document any occurrence of hospitalizations, surgeries, death, malignancies, and/or

CHF annually via a paper questionnaire or eCRF beginning at Year 6 through Year 10. Completed questionnaires will be entered into the database.

The Physician(s)/institution(s) will permit registry-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.0 Data Analysis Plan

The primary objective of this registry is to evaluate the long-term safety of Humira. The secondary objective of this registry is to evaluate the long-term effectiveness of Humira. See Section 5.0 for complete objectives.

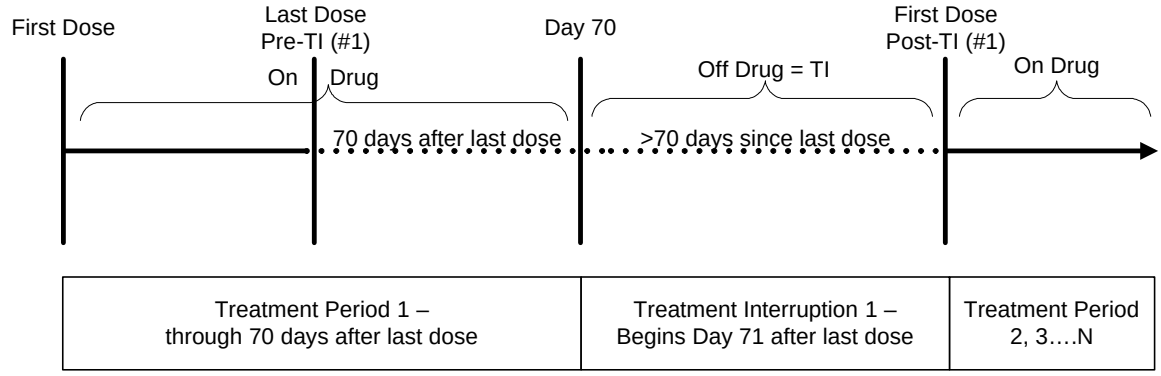
10.1 Analyzable Populations

The All Treated Population is defined as patients who receive at least one dose of MTX or Humira in the registry. The All Treated Population will be used for analysis of safety and effectiveness.

In addition, the Intermittent Treatment Population, defined as Humira patients who have at least one treatment interruption in Humira dosing, will be used in the analysis of safety and effectiveness.

A treatment interruption (TI) for a patient will be defined as a period of > 70 consecutive days during which a patient does not receive any Humira injections. The first day of the TI will begin 71 days after the previous injection of Humira. For patients who receive another Humira injection after the TI, the last day of the TI will be defined as the day before the patient receives the next injection (i.e., the first post-TI Humira injection; see Figure 3). Note that a patient may have multiple TIs. If a patient fails to restart Humira within 1 year of the last Humira injection, then that patient will not be included in the Intermittent Treatment Population.

Figure 3. Treatment Period and Treatment Interruption (TI) Period



10.2 Demographics and Registry Enrollment Characteristics

Baseline characteristics: age, sex, race/ethnicity, weight, height, duration of JIA, JIA disease activity and onset type of JIA Disease onset, Rheumatoid factor (RF+, RF-), HLA-B27, body mass index (BMI), prior therapies for JIA, concomitant polyarticular JIA medications, and Humira dosage and exposure duration.

Demographics and baseline characteristics will be summarized for the All Treated Patient Population. Descriptive statistics for demographics, effectiveness, and safety parameters will be presented. Number of patients with non missing values, mean, and standard deviation will be provided for continuous variables. Counts and percentages will be provided for categorical variables. The number and percentage of patients who discontinue from the registry will be summarized, overall and by reason for discontinuation. Duration of observation in the registry, registry exposure duration and total exposure duration will be summarized as follows:

- Duration of observation period = the last date of registry participation (inclusive of HCP process) – enrollment date to MTX or Humira in the registry + 1
- Registry exposure duration:

- (MTX arm) = last MTX dose date in the registry or the first Humira dose date in the registry whichever is earlier – first MTX dose date in the registry + 1 (The first MTX dose in the registry will be on or after the enrollment date).
- (Humira arm) = last Humira dose date in the registry – first Humira dose date in the registry + 14 days – total days of any treatment interruptions (The first Humira dose in the registry will be on or after the enrollment date).

- Total exposure duration:
  - (MTX arm) = last MTX dose in the registry or the first Humira dose date in the registry whichever is earlier – first recorded MTX dose (initial dose) + 1.
  - (Humira arm) = last Humira dose date in the registry – first recorded Humira dose (initial dose) + 14 – total days of any treatment interruptions. For patients who rolled over from Study DE038 and were in the Placebo arm during the double-blind period of this study, the duration of the double-blind period will be subtracted from total exposure.

10.3 Safety Analyses

Four safety summaries will be reported from this registry.

- Observational AEs: SAEs and AEs of Special Interest occurring from the first day in registry through the last contact (see definition in Section 10.3.1) irrespective of drug treatment duration.
- Registry Treatment-Emergent AEs: SAEs and AEs of Special Interest occurring from the first dose in the registry through the last dose plus 70 days in the registry, excluding AEs occurring during TI period.
- All Treatment Emergent AEs: SAEs and AEs of Special Interest occurring from the first recorded dose (initial dose) of MTX or Humira through the last dose plus 70 days in the registry, excluding AEs occurring during TI period. For patients enrolled from Study M10-444 and Study DE038, the total number of SAEs and AEs of Special Interest will include the events reported after the

first recorded dose of study drug in previous study, except those which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period, any events reported by retrospective data collection, and events reported during this registry.

- AEs for intermittent treatment: SAEs and AEs of Special Interest in the Intermittent Treatment Population through 10 years of the registry.

10.3.1 Analysis of Observational SAEs and AEs of Special Interest

The number and percent of patients experiencing SAEs and AEs of Special Interest during the registry, regardless of whether the AEs are reported during or after the Humira or MTX treatment, will be tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. Rates (event per 100 patient year of observation) of SAEs and AEs of Special Interest and the 95% confidence interval will be provided. The AEs summaries will also include SAEs and AEs of Special Interest collected through the HCP process. The last contact date is defined as the last date of registry or direct to HCP process participation, whichever occurs later.

The summaries will be provided using data from the first day in registry through the last contact irrespective of drug treatment duration.

10.3.2 Analysis of Registry Treatment-Emergent SAEs and AEs of Special Interest

Registry Treatment-emergent SAEs and AEs of Special Interest will be summarized.

Registry Treatment-emergent AEs includes AEs occurring from the first dose day of the registry to 70 days after the last dose of registry drug excluding AEs occurring during TI period. The SAEs and AEs of Special Interest collected through the HCP process will not be included in this summary.

The number and percentage of patients experiencing registry treatment-emergent SAEs and AEs of Special Interest will be tabulated by body system and MedDRA® preferred

term. In addition, a summary of SAEs and AEs of Special Interest by severity and relationship to registry drug will be presented. Rates (event per 100 patient-years of registry exposure to Humira or MTX) of SAEs and AEs of Special Interest and the 95% confidence interval will be provided.

10.3.3 Analysis of All Treatment-Emergent SAEs and AEs of Special Interest

All Treatment-emergent SAEs and AEs of Special Interest includes events occurring after the first recorded (initial) dose of MTX or Humira (after the first recorded dose of study drug in previous study for subjects who rollover from Study DE038 or Study M10-444 into this registry), up to 70 days after the last dose of registry drug (excluding SAEs and AEs of Special Interest occurring during TI period and AEs which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period). The SAEs and AEs of Special Interest collected through the HCP process will not be included in this summary.

The number and percentage of patients experiencing treatment-emergent SAEs and AEs of Special Interest will be tabulated by body system and MedDRA® preferred term. In addition, a summary of SAEs and AEs of Special Interest by severity and relationship to registry drug will be presented. Rates (event per 100 patient-years of total exposure to Humira or MTX) of SAEs and AEs of Special Interest and the 95% confidence interval will be provided.

10.3.4 Analysis of Patients with Treatment Interruption (TI)

The following summaries will be performed for patients with a treatment interruption (TI) in Humira injections. The SAEs and AEs of Special Interest collected through the HCP process will not be included in these summaries.

For the first group of safety summaries, all patients will be categorized into 2 groups: patients who have at least one TI and patients who have no TI. Two summaries of SAEs

and Adverse Events of Special Interest will compare descriptively patients who have at least one TI and patients who have no TIs:

- Crude incidence: The number and percent of patients experiencing SAEs or Adverse Events of Special Interest will be tabulated for each SOC and PT.
- Events per 100 patient years of observation: The number of SAEs and Adverse Events of Special Interest per 100 patient years of observation will be tabulated for each SOC and PT.

For the second group of safety summaries the longest TI will be considered and adverse event rates (SAE and Adverse Events of Special Interest) during the last on-drug period prior to the TI (i.e., the pre-TI period) will be compared to adverse event rates during the first on drug period following the TI (i.e., the post-TI period).

Table 2. Definition of Pre-TI and Post-TI Periods

	Pre-TI Period	Post-TI Period
Start	First injection of the registry	Day of first injection following the longest TI
End	70 days following the last injection before the longest TI	70 days following registry completion/stop of participation

The preceding summaries do not distinguish between the same adverse events experienced by the same patients pre-TI and post-TI from the same adverse events experienced by different patients pre-TI and post-TI. Therefore, a third summary will evaluate the proportions of patients who report onset of the same adverse event pre-TI and post-TI, patients who report onset only pre-TI, patients who report onset only post-TI, and patients who do not report the event in either period.

For each TI experienced by ≥ 1% of patients and for each SAE and Adverse Event of Special Interest, the number and percent of patients who have the event or not before the TI and after the TI will be summarized as shown in Table 3. This assessment will provide information about whether same or different patients experience the adverse pre-TI and post-TI.

Table 3. Sample Shift Table for Adverse Events

Adverse Event	Adverse Event Post-TI	
Pre-TI	Yes	No
Yes	N (%)	N (%)
No	N (%)	N (%)

Additionally, summaries of the same patient's safety information before and after TI will be provided.

10.3.5 Analysis of Laboratory Values, Vital Signs, Tanner Maturation Staging

Laboratory values and vital signs, when available, will be summarized by visit; shift tables will be presented for ANA and Tanner Staging showing the change from appropriate baseline.

10.4 Effectiveness Analyses

Effectiveness data will be analyzed as observed, as this is an observational registry. The number of patients with non-missing baseline and visit values, baseline mean, visit mean, mean and standard deviation of change from baseline will be provided for continuous variables. Counts and percentages will be provided for categorical variables.

The effectiveness data will be summarized for the All Treated Patient Population (from the first dose in the registry).

The baseline measurements used in the effectiveness tables for this registry are measurements on or before the first day in the registry, except that for the subjects who are rolled over from a prior AbbVie study (Study DE038 and Study M10-444), the baseline measurements will be the baseline measurements collected in the prior study (Study DE038 and Study M10-444).

10.4.1 Juvenile Idiopathic Arthritis Core Set of Variables

Each of the following core polyarticular JIA component scores, change from the Baseline will be summarized by summary statistics (number of patients, mean, 95% confidence interval, standard deviation, first quartile, median, third quartile, minimum, maximum) at each visit:

a. Physician's global assessment of patient's disease activity by visual analog scale (VAS) (100 mm VAS, 0 = very good and 100 = very bad)
b. Parent's global assessment of patient's disease activity by VAS (100 mm VAS, 0 = very well and 100 = very bad)
c. Number of active joints (joints with swelling not due to deformity or joints with limitation of passive motion [LOM] and with pain and/or tenderness)
d. Number of joints with LOM
e. Disability Index of Childhood Health Assessment Questionnaire (DICHAQ)
f. CRP or ESR if collected and available only when part of the physician's site routine care.

10.4.1.1 Definition PedACR30 Response

A PedACR30 response will be defined as:

- ≥ 30% improvement in at least three of the six polyarticular JIA core set variables and
- ≥ 30% worsening in not more than one of the six remaining polyarticular JIA core set criteria.

The percent change will be calculated as:

$$100 \times (\text{Value} - \text{Baseline})/\text{Baseline}.$$

Improvement of a core set of variables by ≥ 30% is defined as a percent change from Baseline less than equal to –30% and worsening of a core set of variables by ≥ 30% is defined as a percent change from Baseline greater than or equal to 30%.

10.4.1.2 Definition of PedACR 50 and PedACR 70 and PedACR 90 Response

PedACR50, 70 and 90 levels of response will be defined by using improvement percentages of 50, 70 and 90, respectively, in at least 3 of the 6 core set parameters with worsening of 30% or more in no more than 1 of the 6 core set parameters. The effectiveness individual indicators and the PedACR30/50/70/90 response will be summarized descriptively at each registry time point (Figure 1 and Figure 2).

10.4.1.3 Definition of JADAS

The juvenile arthritis disease activity score (JADAS)[18] is defined as the sum of the scores of its four components. The four components are:

a. Physician's global assessment of patient's disease activity measured on 0 – 10 cm VAS
b. Parent's global assessment of patient's disease activity measured on a 0 – 10 cm VAS
c. Number of active joints (joints with swelling not due to deformity or joints with limitation of motion [LOM] and with pain on passive motion, tenderness or both)
d. Normalized ESR or CRP if collected and available only when part of the physician's site routine care.

10.4.1.4 Other Analyses

Child Health Questionnaire (CHQ-PF50; health-related qualify of life) response will also be summarized at each visit, and will be used in exploratory analyses. The analyses of inactive disease assessment, uveitis assessment, swollen joint count and tender joint count will be provided. For patients being enrolled from AbbVie clinical Study DE038 or

Study M10-444, baseline will be defined as the last non-missing observation on or before the date of enrollment in the registry since these assessments were not collected in Study DE038 or not collected in Study M10-444 or not collected in both studies. Details will be provided in the SAP.

10.4.2 Analysis of Effectiveness for Intermittent Treatment with Humira

The objective for analyses of pre-TI and post-TI effectiveness is to determine whether patients can recover pre-TI effectiveness once Humira treatment is reinitiated after the treatment interruption. The analytic approach is based on results from the polyarticular JIA development program which demonstrated that most of the efficacy of Humira in polyarticular JIA is achieved within 12 weeks after initiating treatment.

Effectiveness analyses will be performed only with patients who complete at least 12 weeks of treatment before the TI. Patients need to have at least one visit collecting effectiveness data after the TI. Effectiveness variables will be summarized at 12 weeks after the first dose of the pre TI period and compared to the results at 12 weeks after the first dose of the post-TI period.

If effectiveness results are not available at 12 weeks post-TI, then:

- For patients whose last effectiveness assessment is before Week 12 of the post-TI period, the last post-TI effectiveness assessment prior to discontinuation will be carried forward.
- For patients whose last effectiveness assessment is after Week 12 of the post-TI period, the first post-TI effectiveness assessment after Week 12 will be used.

A comparison of the best response (measured by PedACR 30) in the same patient before and after TI will be provided.

10.5 Interim Analyses

Safety Assessments will be completed periodically, and at the end of the registry, on all cumulative data at specific time points. The timing and content of the interim safety assessments will be based on decisions from Regulatory Agencies, from the Steering Committee meetings and the Publication Plan. Effectiveness analyses may also be included in the Interim Reports as deemed appropriate.

10.6 Determination of Sample Size

The proposed sample size for this registry is approximately 800 patients. Due to the low incidence and prevalence of the disease, the size of the registry has been chosen based on the expected availability of eligible patients to be enrolled in a three year time frame. The estimated recruitment rates were based on published articles and advice from one leading pediatric rheumatology site.

It is planned that a total of 800 patients will be enrolled to this registry in a ratio of 5:3 corresponding to the Humira arm or the MTX arm respectively. The sample size determination is based on the rate of serious infectious AEs in the Humira arm. Assuming a total of 500 patients with full 5 years of follow up in the Humira arm, a maximum total exposure to the Humira in this registry can be 2500 patient years. Typically a higher rate of dropout is expected in a registry compared to traditional controlled studies. Allowing for approximately 68% dropout, a total of approximately 1500 patient years exposure in the Humira arm will have approximately 97% power, using a two-sided test at level of significance $\alpha = 0.05$, to detect a rate of serious infectious AE of 4.8 events per 100 patient years from the rate of 2.8 events per 100 patient years previously seen in this population in Study DE038.

Due to low frequencies of malignancies and congestive heart failure (CHF), patients will be followed for an additional 5 years.

11.0 Final Report and Publications

11.1 Use of Information

At the end of the registry, a final registry report will be written. This report will contain a description of the objectives of the registry, the methodology of the registry and its results and conclusions. The completed CRFs and the registry report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this registry may be published by AbbVie or by any one of the participating physicians after agreement with AbbVie.

11.2 Internet Sites

Information regarding this registry may be posted on various internet websites and will maximally include registry name, number, general population to be enrolled, entrance qualifications, brief description of the registry, registry objectives, doses, accruing physicians (upon their approval) and number of patients to be enrolled.

12.0 Completion of the Registry

AbbVie will select the signatory Investigator from the Investigators who participate in the registry. Selection criteria for this Investigator will include level of participation as well as significant knowledge of the clinical research, investigational, (non interventional Registry) drug and the registry protocol. The signatory Investigator for the registry will review and sign the final report in accordance with the EMA Guidance on Investigator's Signature for Study Reports.

The end-of-registry is defined as the date of the last patient's visit in the registry or direct to HCP process, whichever occurs later.

The Physician will conduct this registry in compliance with the protocol and all applicable regulatory and legal requirements. AbbVie may terminate this registry at any time, either in its entirety or at a site, for reasonable cause provided that written notice is submitted at

a reasonable time in advance of the intended termination. The Physician may also terminate the registry at their site for reasonable cause, after providing written notice to AbbVie a reasonable time in advance of the intended termination.

13.0 Investigator's Agreement

1. I have read this protocol and agree that the registry is ethical.
2. I agree to conduct the registry as outlined and in accordance with all applicable regulations and guidelines.
3. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
4. I have reviewed the local prescribing information for Humira (adalimumab) and MTX (methotrexate).

Protocol Title: A Long-term, Multi-center, Longitudinal Post-marketing, Observational Registry to Assess Long-term Safety and Effectiveness of HUMIRA® (Adalimumab) in Children with Moderately to Severely Active Polyarticular or Polyarticular-course Juvenile Idiopathic Arthritis (JIA) – *STRIVE*

Protocol Date: 05 April 2016

Signature of Principal Physician | Date

Name of Principal Physician (printed or typed)

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

aCL	Anticardiolipin Antibodies
ACR	American College of Rheumatology
AE	Adverse Event
AESI	Adverse Events of Special Interest
ANA	Antinuclear Antibody
AS	Ankylosing Spondylitis
BD	Beçhet's Disease
CHF	Congestive Heart Failure
CHQ	Child Health Questionnaire
CPK	Creatine Phosphokinase
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-reactive Protein
CTC	Common Toxicity Criteria
DICHAQ	Disability Index of Childhood Health Assessment Questionnaire
DMARD	Disease-modifying Antirheumatic Drug
eCRF	Electronic Case Report Form
EMEA	European Medicines Evaluation Agency
ERA	Enthesitis-Related Arthritis
eSAE	Electronic Serious Adverse Event
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HCP	Health Care Provider
HS	Hidradenitis Suppurativa
ICH	International Conference on Harmonization
IEC/EC	Independent Ethics Committee/Ethics Committee
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent-to-treat

JIA	Juvenile Idiopathic Arthritis
JRA	Juvenile Rheumatoid Arthritis
LA	Lupus Anticoagulants
LOM	Limitation of Passive Motion
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTX	Methotrexate
nr-axSPA	Non-radiographic axial spondyloarthritis
NSAID	Nonsteroidal Anti-inflammatory Drug
PedACR	Pediatric ACR
PMOS	Post-marketing Observational Study
POM	Pain on Passive Motion
Ps	Psoriasis
PsA	Psoriatic Arthritis
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDCF	Supplemental data clarification form
TB	Tuberculosis
TNF	Tumor Necrosis Factor
UBC	United BioSource Corporation
UC	Ulcerative Colitis
ULN	Upper Limit of Normal
US	United States
VAS	Visual Analog Scale

Appendix B. List of Protocol Signatories

Appendix C. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the regulations of the U.S. Food and Drug Administration (FDA). The responsibilities imposed upon Investigators by the FDA are summarized in the "Statement of Investigator" (Form FDA 1572), which is a form letter addressed to the sponsor (AbbVie), summarizing the Investigator's qualifications for the registry and his/her willingness to follow FDA regulations with respect to the registry.

In signing a Form FDA 1572, the Investigator agrees to assume the following responsibilities:

1. To conduct the registry(ies) in accordance with the relevant, current protocol(s) and only make changes in a protocol after notifying AbbVie, except when necessary to protect the safety, rights, or welfare of subjects.
2. To personally conduct or supervise the described investigation(s).
3. To inform any subjects, or any persons used as controls, that the drugs are being used for investigational purposes and to ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) review and approval in 21 CFR Part 56 are met.
4. To report to AbbVie adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.
5. To read and understand the information in the Investigator's Brochure, including the potential risks and side effects of the drug.
6. To ensure that all associates, colleagues, and employees assisting in the conduct of the registry(ies) are informed about their obligations in meeting the above commitments.

7. To maintain adequate and accurate records of the conduct of the registry and make those records available for inspection by representatives of AbbVie, the IRB and/or the appropriate regulatory agency, and to notify AbbVie when no longer able to retain the registry-related documents.
8. To ensure that an IEC/IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation.
9. To promptly report to the IEC/IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others (including submission of any Expedited Safety Reports received from AbbVie to the IEC/IRB), and to make no changes in the research without IEC/IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.
10. To comply with all other requirements regarding the obligations of Clinical Investigators and all other pertinent requirements in 21 CFR Part 312.

Appendix D. Pediatric Total Joint Assessment

Joint count: *Score swelling (not due to bony deformity), pain on passive motion (POM), or tenderness as **0** for absence, **1** for presence of symptoms.*

Limitation of motion (LOM): *Score with **0** for absence or **1** for presence of limitation.*

If joint has been replaced/injected, do not score pain/tenderness or swelling. Enter 9 in the "Rep?" column.

→ Unless joint has been replaced/injected, all applicable open boxes must be filled in with **1** or **0**.

		Right					Left				
Item		**Swell**	**POM**	**Tend**	**LOM**	**Rep?**	**Swell**	**POM**	**Tend**	**LOM**	**Rep?**
01	Temp. mand.										
02	Sterno. clav.				n/a	n/a				n/a	n/a
03	Acro. clav.				n/a					n/a	
04	Shoulders										
05	Elbows										
06	Wrist										
07	MCP 1										
08	MCP 2										
09	MCP 3										
10	MCP 4										
11	MCP 5										
12	PIP 1										
13	PIP 2										
14	PIP 3										
15	PIP 4										
16	PIP 5										
17	DIP 2										
18	DIP 3										
19	DIP 4										
20	DIP 5										

Continued on next page

Joint count: *Score swelling (not due to bony deformity), pain on passive motion (POM), or tenderness as **0** for absence, **1** for presence of symptoms,*

Limitation of motion (LOM): *Score with **0** for absence or **1** for presence of limitation.*

If joint has been replaced/injected, do not score pain/tenderness or swelling. Enter 9 in the "Rep?" column.

→ Unless joint has been replaced/injected, all applicable open boxes must be filled in with **0 or 1.**

		Right					**Left**				
Item		**Swell**	**POM**	**Tend**	**LOM**	**Rep?**	**Swell**	**POM**	**Tend**	**LOM**	**Rep?**
21	Hips	n/a					N/a				
22	Knees										
23	Ankles										
24	Subtalar joint	n/a				n/a	N/a				n/a
25	Tarsi										
26	MTP 1										
27	MTP 2										
28	MTP 3										
29	MTP 4										
30	MTP 5										
31	Toes (PIP) 1										
32	Toes (PIP) 2										
33	Toes (PIP) 3										
34	Toes (PIP) 4										
35	Toes (PIP) 5										
36	Sacroiliac	n/a			n/a	n/a	N/a			n/a	n/a
37	Lumbar spine	n/a				n/a					
38	Thoracic spine	n/a				n/a					
39	Cervical spine	n/a				n/a					

n/a = not applicable

Appendix E. Disability Index of Childhood Health Assessment Questionnaire DICHAQ

In this section, we are interested in learning how your child's illness affects his/her ability to function in daily life. Please feel free to add any comments on the back of this page. In the following questions, please check the one response, which best describes your child's usual activities (averaged over an entire day) OVER THE PAST WEEK. ONLY NOTE THOSE DIFFICULTIES OR LIMITATIONS, WHICH ARE DUE TO ILLNESS. If most children at your child's age are not expected to do a certain activity, please mark it as "Not Applicable." For example, if your child has difficulty in doing a certain activity or is unable to do it because he/she is too young but NOT because he/she is RESTRICTED BY ILLNESS, please mark it as "Not Applicable."

	Without ANY Difficulty	**With SOME Difficulty**	**With MUCH Difficulty**	**UNABLE To Do**	**Not Applicable**
DRESSING AND GROOMING					
Is your child able to:					
− Dress, including tying shoelaces and doing buttons?	_____	_____	_____	_____	_____
− Shampoo his/her hair?	_____	_____	_____	_____	_____
− Remove shocks?	_____	_____	_____	_____	_____
− Cut fingernails?	_____	_____	_____	_____	_____
ARISING					
Is your child able to:					
− Stand up from a low chair or floor?	_____	_____	_____	_____	_____
− Get in and out of bed or stand up in crib?	_____	_____	_____	_____	_____
EATING					
Is your child able to:					
− Cut his/her own meat?	_____	_____	_____	_____	_____
− Lift a cup or glass to mouth?	_____	_____	_____	_____	_____
− Open a new cereal box?	_____	_____	_____	_____	_____
WALKING					
Is your child able to:					
− Walk outdoors on flat ground?	_____	_____	_____	_____	_____
− Climb up five steps?	_____	_____	_____	_____	_____

***Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

____ Cane

____ Walker

____ Crutches

____ Wheelchair

____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc)

____ Built up pencil or special utensils

____ Special or built up chair

____ Other (Specify:)

***Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

____ Dressing and grooming

____ Arising

____ Eating

____ Walking

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	Not Applicable
HYGIENE					
Is your child able to:					
− Wash and dry entire body?	_____	_____	_____	_____	_____
− Take a tub bath (get in and out of tub)?	_____	_____	_____	_____	_____
− Get on and off the toilet or potty chair?	_____	_____	_____	_____	_____
− Brush teeth?	_____	_____	_____	_____	_____
− Comb/brush hair?	_____	_____	_____	_____	_____
REACH					
Is your child able to:					
− Reach and get down a heavy object such as a large game or books from just above his/her head?	_____	_____	_____	_____	_____
− Bend down to pick up clothing or a piece of paper from the floor?	_____	_____	_____	_____	_____
− Pull on a sweater over his/her head?	_____	_____	_____	_____	_____
− Turn neck to look back over shoulder?	_____	_____	_____	_____	_____
GRIP					
Is your child able to:					
− Write or scribble with pen or pencil?	_____	_____	_____	_____	_____
− Open car doors?	_____	_____	_____	_____	_____
− Open jars which have been previously opened?	_____	_____	_____	_____	_____
− Turn faucets on and off?	_____	_____	_____	_____	_____
− Push open a door when he/she has to turn a door knob?	_____	_____	_____	_____	_____
ACTIVITIES					
Is your child able to:					
− Run errands and shop?	_____	_____	_____	_____	_____
− Get in and out of car or toy car or school bus?	_____	_____	_____	_____	_____
− Ride bike or tricycle?	_____	_____	_____	_____	_____
− Do household chores (e.g., wash dishes, take out trash, vacuuming, yard work, make bed, clean room)?	_____	_____	_____	_____	_____
− Run and play?	_____	_____	_____	_____	_____

***Please check any AIDS or DEVICES that your child usually uses for any of the above activities:**

____ Raise toilet seat
____ Bathtub bar
____ Bathtub seat
____ Long-handled appliances for reach
____ Jar opener (for jars previously opened)
____ Long-handled appliances in bathroom

***Please check any categories for which your child usually needs help from another person BECAUSE OF ILLNESS:**

____ Hygiene
____ Gripping and opening things
____ Reach
____ Errands and chores

Appendix F. Visual Analog Scale (VAS)

PHYSICIAN'S GLOBAL ASSESSMENT OF DISEASE ACTIVITY:

Very Good	Very Bad
0	100

Parents:

PAIN: We are interested in learning whether or not your child has been affected by pain because of his or her illness. By placing a single mark on the line below, indicate how much pain you think your child has had because of his or her illness IN THE PAST WEEK?

No Pain	Very Severe Pain
0	100

GLOBAL EVALUATION: Considering all the ways arthritis affects your child, rate how he/she is doing by placing a single mark on the line below.

Very Well	Very Poor
0	100

Appendix G. Child Health Questionnaire

CHILD HEALTH QUESTIONNAIRE (CHQ-PF50)

PARENT FORM – 50 ENGLISH (U.S.)

ID NUMBER

TODAY'S DATE

MONTH / DAY / YEAR

INSTRUCTIONS: This form asks about your child's health and well-being. Your responses will be treated confidentially. There are no right or wrong responses. If you are unsure how to respond to a question, give the best response you can. It is important that you fill in each question. Please use blue or black ink.

Correct Marks: ■ ☒ ☑ ✒

SECTION 1: YOUR CHILD'S GLOBAL HEALTH

		Excellent	Very good	Good	Fair	Poor
1.1.	In general, would you say your child's health is:	☐	☐	☐	☐	☐

SECTION 2: YOUR CHILD'S PHYSICAL ACTIVITIES

The following questions ask about physical activities your child might do during a day.

		Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
2.1.	During the past 4 weeks, has your child been limited in any of the following activities due to health problems?				
	a. Doing things that take a lot of energy, such as playing soccer, or running?	☐	☐	☐	☐
	b. Doing things that take some energy such as riding a bike or skating? ☐	☐	☐	☐	
	c. Ability (physically) to get around the neighborhood, playground, or school?	☐	☐	☐	☐
	d. Walking one block or climbing one flight of stairs?	☐	☐	☐	☐
	e. Bending, lifting, or stooping?	☐	☐	☐	☐
	f. Taking care of him/herself, that is, eating, dressing, bathing, or going to the toilet?	☐	☐	☐	☐

SECTION 3: YOUR CHILD'S EVERYDAY ACTIVITIES

		Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
3.1.	During the past 4 weeks, has your child's school work or activities with friends been limited in any of the following ways due to EMOTIONAL difficulties or problems with his/her BEHAVIOR?				
	a. Limited in the KIND of schoolwork or activities with friends he/she could do	☐	☐	☐	☐
	b. Limited in the AMOUNT of time he/she could spend on schoolwork or activities with friends	☐	☐	☐	☐
	c. Limited in PERFORMING schoolwork or activities with friends (it took extra effort)	☐	☐	☐	☐

		Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
3.2.	During the past 4 weeks, has your child's school work or activities with friends been limited in any of the following ways due to problems with his/her PHYSICAL health?				
	a. Limited in the KIND of schoolwork or activities with friends he/she could do	☐	☐	☐	☐
	b. Limited in the AMOUNT of time he/she could spend on schoolwork or activities with friends	☐	☐	☐	☐

SECTION 4: PAIN

4.1. During the past 4 weeks, how much bodily pain or discomfort has your child had?

None	Very mild	Mild	Moderate	Severe	Very severe
☐	☐	☐	☐	☐	☐

4.2. During the past 4 weeks, how often has your child had bodily pain or discomfort?

None of the time	Once or twice	A few times	Fairly often	Very often	Every/almost every day
☐	☐	☐	☐	☐	☐

SECTION 5: BEHAVIOR
Below is a list of items that describe children's behavior or problems they sometimes have.

5.1. How often during the past 4 weeks did each of the following statements describe your child?

	Very often	Fairly often	Some-times	Almost never	Never
a. Argued a lot?	☐	☐	☐	☐	☐
b. Had difficulty concentrating or paying attention?	☐	☐	☐	☐	☐
c. Lied or cheated?	☐	☐	☐	☐	☐
d. Stole things inside or outside the home?	☐	☐	☐	☐	☐
e. Had temper tantrums or a hot temper?	☐	☐	☐	☐	☐

5.2 Compared to other children your child's age, in general would you say his/her behavior is:

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

SECTION 6: WELL-BEING
The following phrases are about children's moods.

6.1. During the past 4 weeks, how much of the time do you think your child:

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Felt like crying?	☐	☐	☐	☐	☐
b. Felt lonely?	☐	☐	☐	☐	☐
c. Acted nervous?	☐	☐	☐	☐	☐
d. Acted bothered or upset?	☐	☐	☐	☐	☐
e. Acted cheerful?	☐	☐	☐	☐	☐

SECTION 7: SELF-ESTEEM

The following ask about your child's satisfaction with self, school, and others. It may be helpful if you keep in mind how other children your child's age might feel about these areas.

7.1. During the past 4 weeks, how satisfied do you think your child has felt about:

	Very satisfied	Somewhat satisfied	Neither satisfied nor dissatisfied	Somewhat dissatisfied	Very dissatisfied
a. His/her school ability?	☐	☐	☐	☐	☐
b. His/her athletic ability?	☐	☐	☐	☐	☐
c. His/her friendships?	☐	☐	☐	☐	☐
d. His/her looks/appearance?	☐	☐	☐	☐	☐
e. His/her family relationships?	☐	☐	☐	☐	☐
f. His/her life overall?	☐	☐	☐	☐	☐

SECTION 8: YOUR CHILD'S HEALTH

The following statements are about health in general.

8.1. How true or false is the statement for your child?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. My child seems to be less healthy than other children I know	☐	☐	☐	☐	☐
b. My child has never been seriously ill	☐	☐	☐	☐	☐
c. When there is something going around my child usually catches it	☐	☐	☐	☐	☐
d. I expect my child will have a very healthy life	☐	☐	☐	☐	☐
e. I worry more about my child's health than other people worry about their children's health	☐	☐	☐	☐	☐

8.2 Compared to one year ago, how would you rate your child's health now:

Much better now than 1 year ago	Somewhat better now than 1 year ago	About the same now as 1 year ago	Somewhat worse now than 1 year ago	Much worse now than 1 year ago
☐	☐	☐	☐	☐

SECTION 9: YOU AND YOUR FAMILY

9.1. During the past 4 weeks, how MUCH emotional worry or concern did each of the following cause YOU?

	None at all	A little bit	Some	Quite a bit	A lot
a. Your child's physical health	☐	☐	☐	☐	☐
b. Your child's emotional well-being or behavior	☐	☐	☐	☐	☐
c. Your child's attention or learning abilities	☐	☐	☐	☐	☐

9.2. During the past 4 weeks, were you LIMITED in the amount of time YOU had for your own needs because of:

	Yes, limited a lot	Yes, limited some	Yes, limited a little	No, not limited
a. Your child's physical health?	☐	☐	☐	☐
b. Your child's emotional well-being or behavior?	☐	☐	☐	☐
c. Your child's attention or learning abilities?	☐	☐	☐	☐

9.3. During the past 4 weeks, how often has your child's health or behavior:

	Very often	Fairly often	Sometimes	Almost never	Never
a. Limited the types of activities you could do as a family?	☐	☐	☐	☐	☐
b. Interrupted various everyday family activities (eating meals, watching tv)?	☐	☐	☐	☐	☐
c. Limited your ability as a family to "pick up and go" on a moment's notice?	☐	☐	☐	☐	☐
d. Caused tension or conflict in your home?	☐	☐	☐	☐	☐
e. Been a source of disagreements or arguments in your family?	☐	☐	☐	☐	☐
f. Caused you to cancel or change plans (personal or work) at the last minute?	☐	☐	☐	☐	☐

9.4. Sometimes families may have difficulty getting along with one another. They do not always agree and they may get angry. In general, how would you rate your family's ability to get along with one another?

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

Appendix H. Tanner Maturation Staging

Date of the Visit	
Registry Visit	**Example "Baseline"**
Signature	
Date	

BOYS

Stage	PUBIC HAIR
1	None
2	Scanty, long, slightly pigmented
3	Darker, starts to curl, small amount
4	Resembles adult type, less in quantity; coarse, curly
5	Adult distribution, spread to medial surface of thighs

Sexual development stage:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Stage	GENITALS	
	Penis	Testes
1	Preadolescent	Preadolescent
2	Slight enlargement	Enlarged scrotum, pink texture altered
3	Longer	Larger
4	Larger, glans and breadth increase in size	Larger, scrotum dark
5	Adult	Adult

Sexual development stage:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

GIRLS

Stage	PUBIC HAIR
1	None
2	Sparse, lightly pigmented, straight, medial border of labia
3	Darker, beginning to curl, increased amount
4	Coarse, curly, abundant but amount less than in adult
5	Adult feminine triangle, spread to medial surface of thighs

Sexual development stage:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Stage	BREASTS
1	Preadolescent
2	Breast and papilla elevated as small mound, aureolar diameter increased
3	Breast and areola enlarged. No contour separation
4	Areola and papilla form secondary mound
5	Mature, nipple projects, areola part of general breast contour

Sexual development stage:
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5

Pubertal Growth and Maturation

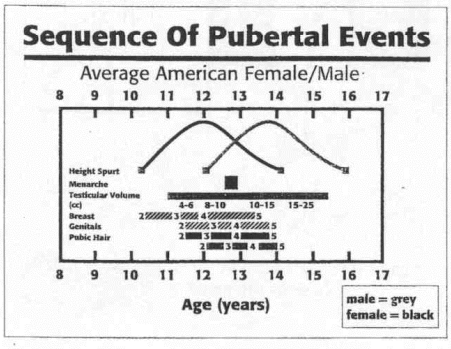
Introduction

Adolescents are in various stages of maturity at any given chronological age. Maturity is inclusive of cognitive, psychosocial and biological or pubertal development. During puberty, the most prominent and dramatic changes are skeletal growth and the development of secondary sexual characteristics. Change also occurs in the brain, endocrine glands, body composition, and fertility status. Puberty affects multiple organ systems, and different organ systems mature at different rates. For example, the nervous system reaches adult size by ten years of age, while the lymphoid system reaches 200% of adult size between 10 to 12 years of age, and then begins to recede in size.

Unlike the early maturation of the nervous system and lymph systems, nearly one-fourth of the total adult height is attained during the pubertal growth spurt. Linear growth, which has been occurring at about 4 to 6 cm per year, slows down just prior to entering puberty. With the onset of puberty, limbs begin growing before the trunk. Growth of distal portions of the limbs is accelerated, beginning before the growth of more proximal parts. This accounts for the expression describing teens as "all hands and feet." In later puberty, the trunk contributes a greater proportion to linear growth. In addition to the growth spurt, secondary sex characteristics begin to appear. This results in the development of breasts and pubic hair in females and the development of pubic hair and testicular and penile growth in males.

Sequence of Pubertal Events

Pubertal changes tend to follow a predictable sequence when looking at a large group, but can be variable in the individual. The age of pubertal changes varies with genetic, socioeconomic, and nutritional factors. The rate of change, tempo, is also fairly consistent for groups, but may vary from one individual to another. Sequence and tempo are two of the most important concepts regarding puberty. Deviation from sequence and tempo suggest factors influencing pubertal maturation.



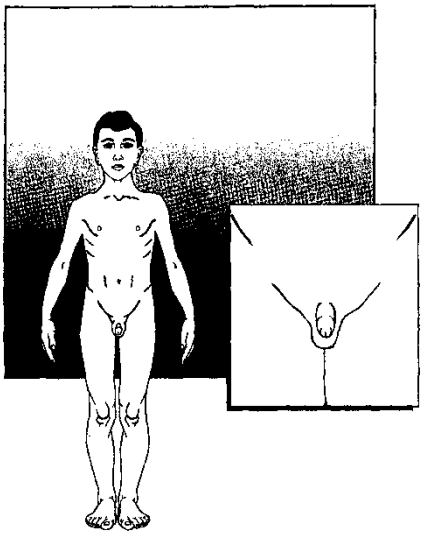
Girls

The average age of onset of puberty in American girls is 10.1 to 10.5 years. Females enter puberty earlier than males do, and thus lose a year or so of the slow but steady pre-pubertal growth. African-American girls tend to enter puberty slightly earlier than Caucasian girls. The first pubertal changes which occur in the female are internal, with ovaries increasing in size. The first outward visible sign of puberty is the development of pubic hair (adrenarche) or breasts (thelarche). Thelarche occurs in 95% of girls between ages 9 and 13 years. The majority of girls (60%) will experience the appearance of breast buds several months prior to the appearance of pubic hair. However, some females will develop pubic hair prior to the development of the breast bud. Soon after onset of puberty, girls will enter their peak height velocity. Menarche generally occurs after the peak height velocity and during the second half of puberty. The average age of menarche in the U.S. is around 12.6 years. Marshall and Tanner describe 5 stages of breast development and 5 stages of pubic hair development. Pubic hair is included as a rating criterion but is less valid than other criteria in assessing sexual maturation, since its appearance is related to adrenal, as well as gonadal development.

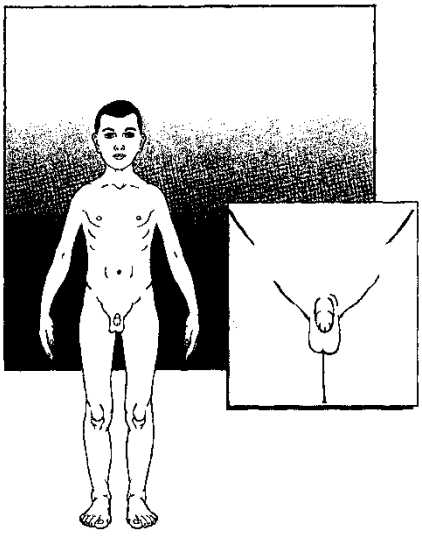
Boys

The average age of onset of puberty in American boys is 12.2 years. Nearly all boys have an increase in testicular volume as the initial sign of puberty, followed 6 to 7 months later by the development of pubic hair. As described by Marshall and Tanner, gonadal development occurs in 5 stages, as does pubic hair development. The peak height velocity generally occurs in the second half of puberty. Spermarche, or the appearance of sperm in the urine, occurs approximately at the same time. Approximately one-half of males will have the transient (under 18 months) appearance of breast tissue (gynecomastia).

GONADAL DEVELOPMENT

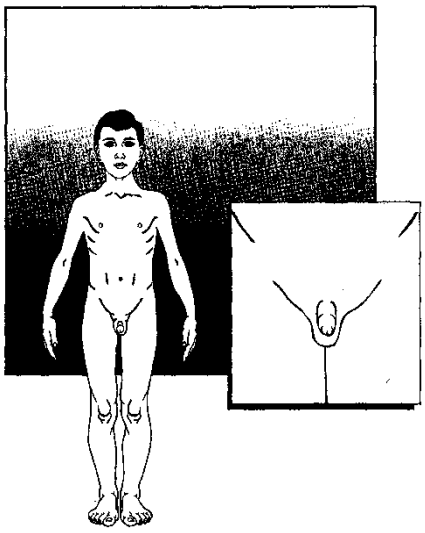


Stage 1: Penis, testes, and scrotum are child-like in appearance and size.

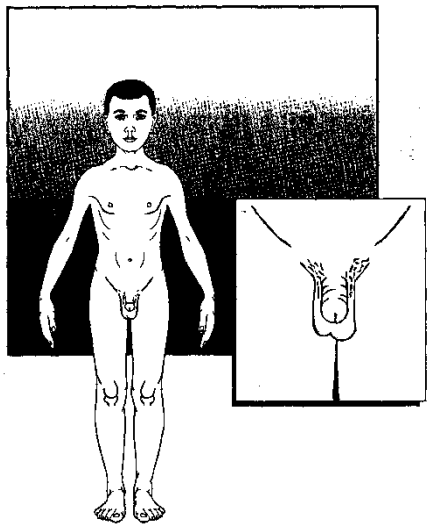


Stage 1a: Early testicular maturation.

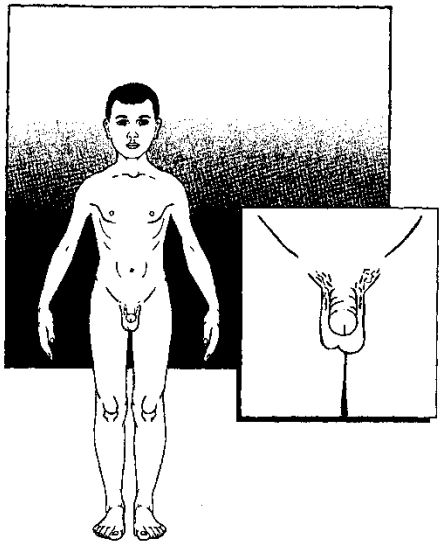
PUBIC HAIR DEVELOPMENT



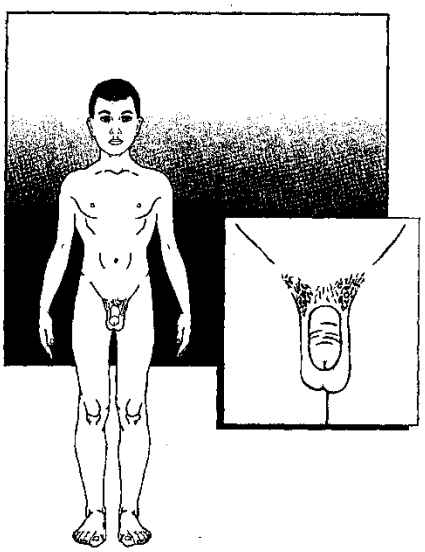
Stage 1: Prepubertal with no pubic hair.



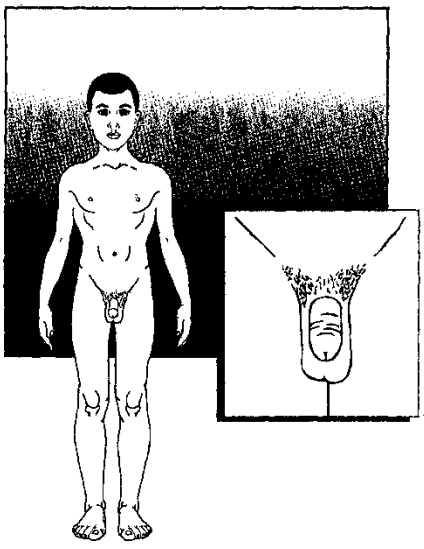
Stage 2: Sparse growth of fine downy hair along the base of the penis.



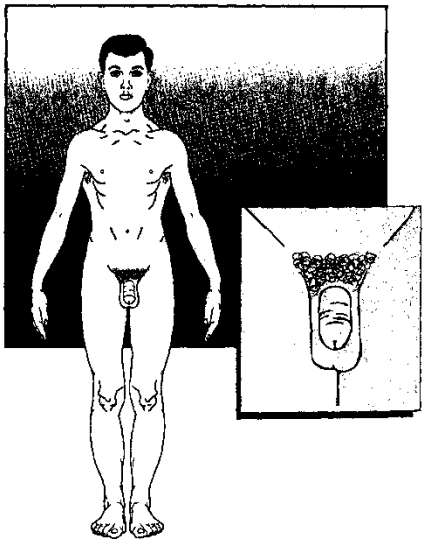
Stage 2: An enlargement of scrotum and testes, but the penis usually does not enlarge. The scrotal skin reddens.



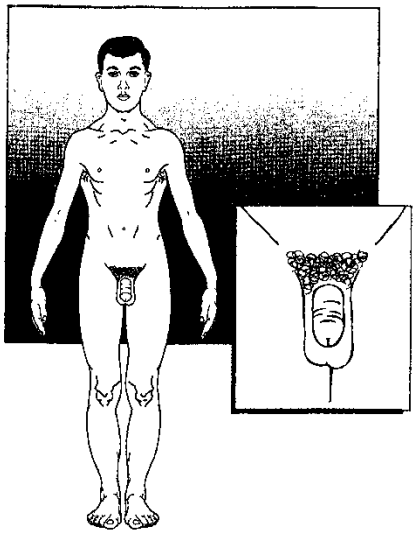
Stage 3: Further growth of testes and scrotum, with enlargement of the penis, mostly in length.



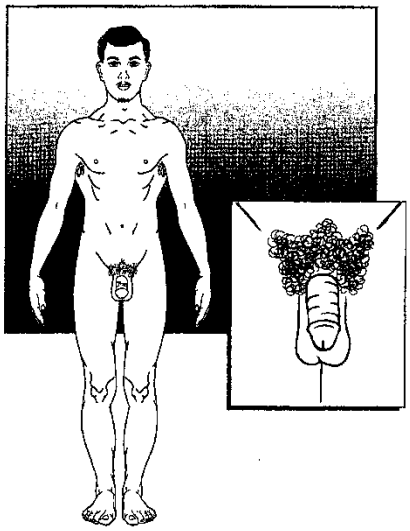
Stage 3: Hair is darker, coarser, and curlier, and extends over the middle of the pubic bone.



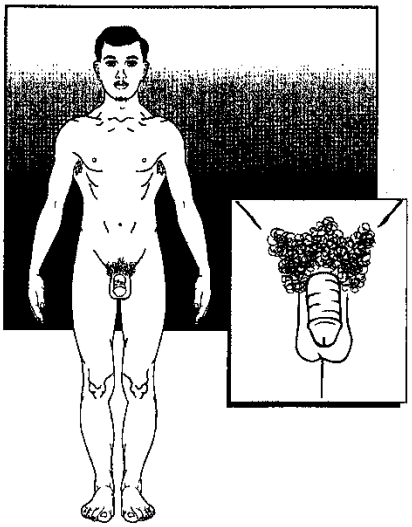
Stage 4: Hair is adult-like in appearance but does not extend to the thighs.



Stage 4: Further growth of the testes and scrotum with an increased size of the penis.



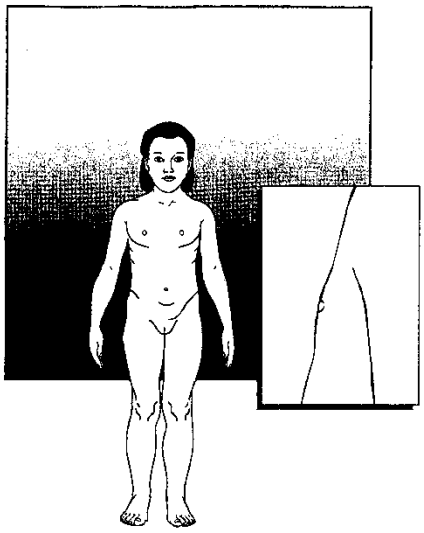
Stage 5: Genitals are adult-like in size. Growth of the penis is generally complete prior to full development of the testes and pubic hair.



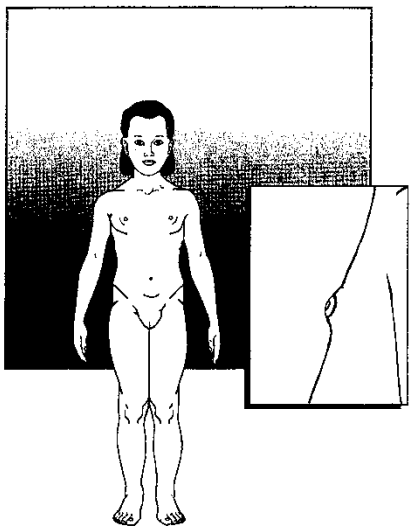
Stage 5: Hair is adult-like in appearance and distribution and extends from thigh to thigh and may extend toward the umbilicus.

NOTES

BREAST DEVELOPMENT

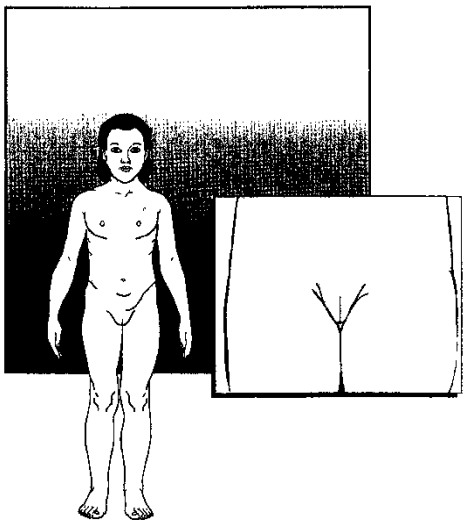


Stage 1: Prepubertal with no noticeable change in size of breast.

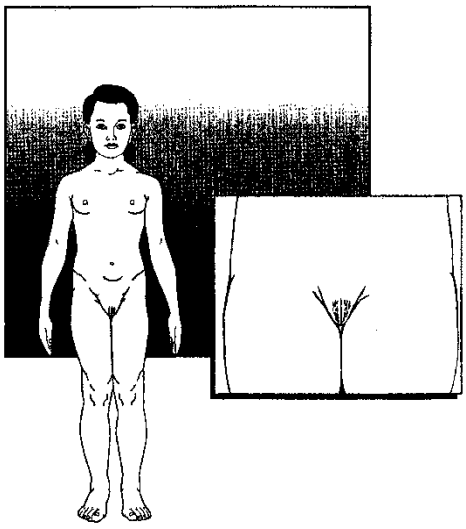


Stage 2: Breast Bud Stage with a small mound formed by the elevation of the breast papilla; areolar diameter enlarges.

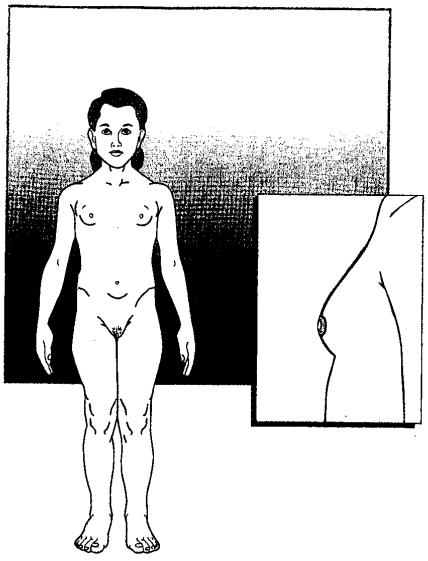
PUBIC HAIR DEVELOPMENT



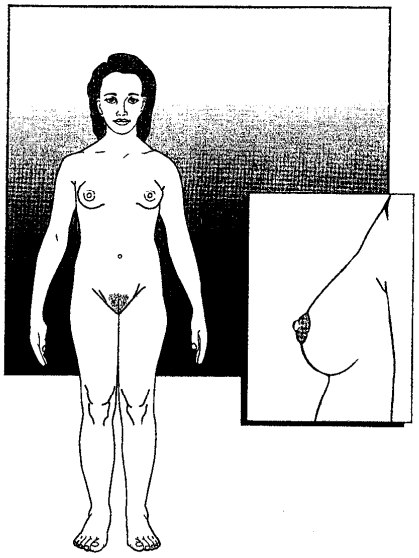
Stage 1: Prepubertal with no pubic hair.



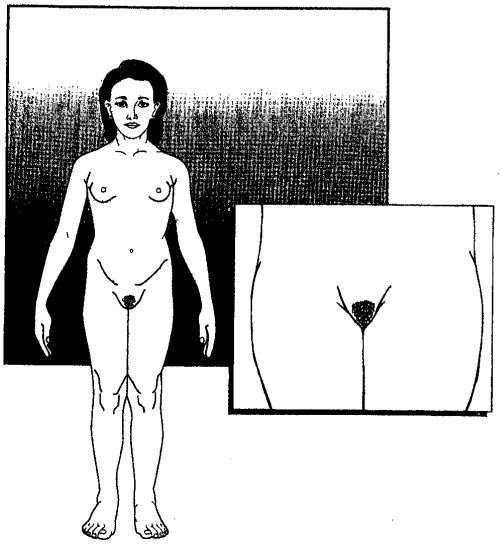
Stage 2: First appearance of hair which is sparse, straight or only slightly curled, long, slightly pigmented, downy, and primarily located along the labia.



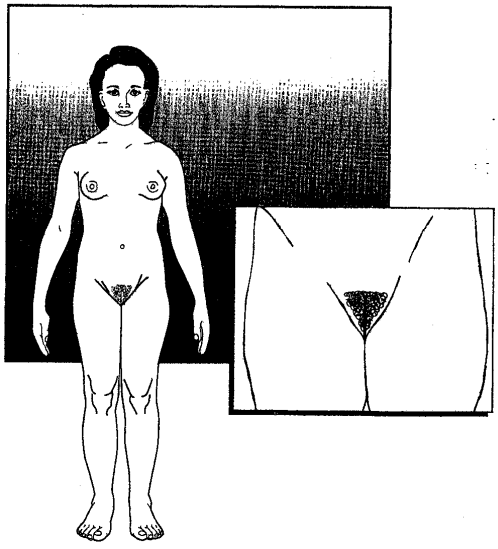
Stage 3: Further enlargement of breast and areola with no separation of their contours.



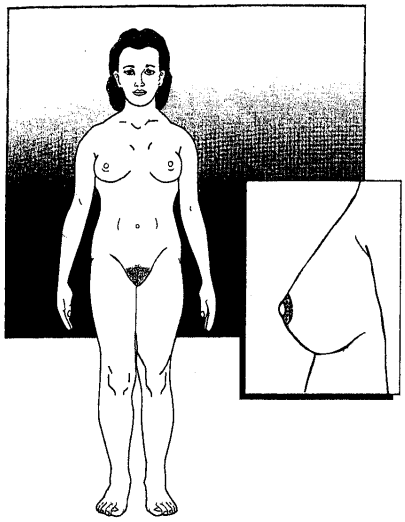
Stage 4: Projection of the areola and papilla which forms a secondary mound above the level of the breast.



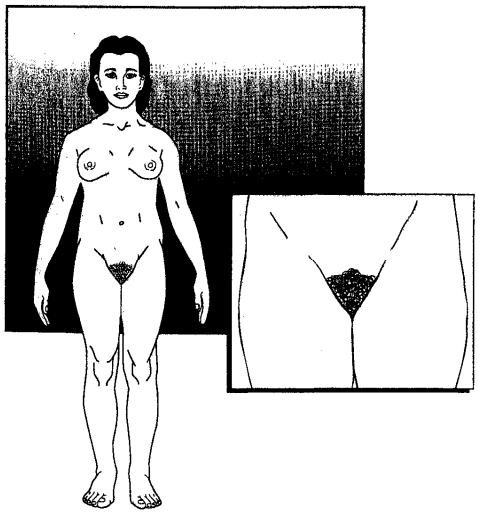
tage 3: Hair is coarser, darker and more curled and spreads over the middle of the pubic bone.



Stage 4: Hair is adult-like in appearance but not distribution.



Stage 5: Breast is adult-like in appearance, areola recessed to general contour of the breast, accompanied by an increase in the overall size of the breast. Not all women complete this stage.



Stage 5: Hair is adult-like in appearance and distribution with extension onto the thighs. Extension of hair growth in the midline and in the shape of a broad-based triangle. Generally, pubic hair stage 5 is reached prior to breast stage 5.

NOTES

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About the Center for Continuing Education in Adolescent Health (CCEAH)

The Center was funded by the Maternal and Child Health Bureau in 1990 to develop *Basic Concepts in Identifying the Health Needs of Adolescents*, a core adolescent health curriculum for service providers. This piece is based on the first of its eight modules. A second training curriculum, *Obtaining a Sexual History from an Adolescent*, was completed in 1996.

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Daniels WA. Sex maturity ratings. *J Pediatr* 1979; 95:255-256.

Maturity ratings reflect biologic stage of growth with far greater accuracy than chronologic age.

Tanner JM, Davies PS. Clinical longitudinal standards for height and height velocity for North American children. *J Pediatr* 1985; 107:317-329.

Cross-sectional data cannot follow the growth of individual children once puberty has begun; the 50th centile line derived from cross-sectional data is not actually followed by an individual child, and is not the correct shape for a growth curve. Paper gives longitudinal data, also stratified by early, mid, and late maturers. These charts refer to whole-year velocities; velocities calculated over shorter periods (<.85 yrs.) reflect seasonal effects (most children grow faster in the spring and slower in the fall) and are relatively more affected by the unavoidable errors in measurement.

Backous DD, Farrow JA, Friedl KE. Assessment of pubertal maturation in boys, using height and grip strength. *JAHC* 1990; 11:497-500.

Pubertal status suggested to be predictive of specific types of musculoskeletal injuries in adolescents during sports participation. Greater risk of damage at the epiphyseal growth plates in period of peak skeletal growth. Also proposed to be greater risk of sprains, owing to excessive ligamentous laxity, or strains due to excessive tightness during period of peak height velocity and maximal increase in muscle mass. Pubertal maturity is often taken as the measure of physical maturity; however, measures of strength and skeletal height may be better predictors of physical maturity and good endpoint predictors of pubertal maturity.

Peak growth velocity in boys is more closely related to pubertal maturation than to chronologic age (Cf Buckler JMH. Skeletal age changes in puberty. *Arch Dis Child* 1984;59:115-9), because height in adolescent boys is highly correlated with testosterone levels (e.g., Nottlemann ED, Susman EJ et al *JAHC* 1987; 8:246-260). Data in this paper suggests that there is a group of taller and generally pubertally mature boys who do not yet possess the muscular strength of peers of similar height. An increased injury incidence has already been documented for subpopulation playing soccer (Cf Backous DD, Friedl KE. *AJDC* 1988; 142:839-842).

Petersen AC. Adolescent development. *Ann Rev Psychol* 1988; 39:583-607.

Review article: advancing pubertal status was related to enhanced body image and improved mood for boys, but decreased feelings of attractiveness for girls (Crockett and Petersen, 1987). Pubertal change is most stressful when it puts the early adolescent in a deviant status relative to his/her peers, or when changes not seen as advantageous or desirable (Simmons et al, 1983). In girls, pubertal events noticeable by others (e.g., height and breast development) are more likely to affect psychological functioning than non-public changes (e.g., pubic hair growth) (Brooks-Gunn and Warren, 1988). Pubertal hormones may affect behavior of boys, particularly aggression (Susman, vide infra); may also affect sexual interest (e.g., Udry). Most of the observed effects, however, appear to be mediated by or interact with social and psychological factors (Brooks-Gunn presentation listed, 1988).

Wheeler MD. Physical changes of puberty. *Endo and Metab Clin No Amer* 1991; 20:1-14.

Females: many observers combine the breast and pubic hair standards into one staging; 15% of normal girls develop pubic hair before breast enlargement. Girls lose fat only from the upper arm, although there is a slowing of fat accumulation on the thigh and calf. Males: adrenal androgens may account for some pubic hair development or even phallic growth in extreme cases; best to describe genital stage separately from pubic hair stage. Right testicle generally larger than left. Close concordance between pubic hair and genital stages in boys, and no differences between blacks and whites (ref. Harlan WR, Grillo GP, Comoni-Huntleyj, et al. Secondary sexual characteristics of boys 12 to 17 years of age: The U.S. health examination survey. *J Pediatr* 1979; 95:293).

Tanner JM. Issues and advances in adolescent growth and development. *J Adol Health Care* 1987; 8:470-478.

Tempo and ultimate size are entirely unrelated in normal children. Long-acting synthetic analogue of GnRH now used for precocious puberty; turns off puberty mechanism, with regression of maturation. Various sequences of events at puberty-growth spurt, breast development, pubic hair development, bone age progression, change in body composition-linked to varying degrees. Closest link between bone age and occurrence of menarche; age at peak height velocity and age at menarche also closely linked.

Orr DP, Brack CJ Ingersoll G. Pubertal maturation and cognitive maturity in adolescents. *J Adol Health Care* 1988; 9:273-279.

When effects of age are controlled, more advanced (self-assessed) Tanner stage was not a predictor of more mature cognitive processes.

the published criteria are clearly noted, lest they result in inability to interpret and compare the reported data. It is a requirement, for example, for classification in the polyarthritis rheumatoid positive category, that RF be present on 2 occasions at least 3 months apart. This was intended to make certain the unrelated RF positivity, such as that which might follow an infection, not be allowed to obscure what was felt to be significant persistent RF test positivity. This may be contrary to usual clinical practice, and has therefore been an impediment to the easy application of the criteria. Although RF testing would be ideally performed during the first 6 months of disease, this may not always be possible, and test results obtained at a later time should then be used. These requirements should be evaluated; the results of such an evaluation may well influence the criteria. The ILAR committee has concluded that until such data are forthcoming, in keeping with the principles adopted by the committee, the requirement for 2 positive tests for RF will be retained in the present revision.

It is anticipated that the proposed classification will undergo further revision in order to correct anomalies, and in response to new information. Such changes would be incorporated if they resulted in a demonstrable and objective improvement in homogeneity of the categories in the classification. The ILAR classification has proved useful in sparking controversy, questions and international debate, and research about JIA. The prospective gathering of new clinical information has been stimulated and will lead to an improved understanding of these diseases.

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Appendix I. Protocol Amendment: List of Changes

Global Protocol Change:

"JIA" previously read "JIA" has been changed to read "polyarticular JIA" when referring to the Humira approved indication and patient population in this registry.

Specific Protocol Changes:

Section 1.0 Title Page
"AbbVie Emergency Contact:" previously read:

[redacted]

Has been changed to read:

[redacted]

Section 3.0 Introduction
Eighth paragraph, last sentence previously read:

Orencia® (abatacept) was approved in the United States (US) for the use in patients with polyarticular JIA 2008 and approved in the EU in 2010.

Has been changed to read:

Orencia® (abatacept) was approved for the treatment of polyarticular JIA in the United States (US) in 2008 and in the EU in 2010.

Section 3.0 Introduction
Ninth paragraph previously read:

Actemra® / RoActemra® (tocilizumab) was approved for systemic onset of JIA in Japan in 2008 and in the EU and the US in 2011.

Has been changed to read:

Actemra®/RoActemra® (tocilizumab) was approved for the treatment of systemic JIA in Japan in 2008 and in the EU and US in 2011, and was approved for treatment of polyarticular JIA in the EU and US in 2013.

Ilaris (canakinumab) is approved for treatment of systemic JIA in the EU and US in 2013.

Section 3.0 Introduction
Twelfth and thirteenth paragraph previously read:

The FDA first approved Humira for the treatment of subjects with RA in the United States (US) in December 2002 and in the European Union (EU) in September 2003. As of 31 December 2012, Humira has been approved for at least one indication in 90 countries worldwide. Additional data were submitted in the US and EU to support claims for Humira treatment of subjects with early RA and those with Psoriasis Arthritis (PsA). Both indications were approved in the EU on 01 August 2005 and in the US on 03 October 2005, respectively. Subsequently, an indication for Ankylosis Spondylitis (AS) was approved in EU on 01 June 2006 and in the US on 28 July 2006. An indication for Crohn's Disease was approved in EU on 04 June 2007 and in the US on 27 February 2007. An indication for psoriasis (PS) was approved in the EU on 19 December 2007 and in the US on 18 January 2008. An indication for Ulcerative Colitis was approved in the EU on 04 April 2012. An indication for Axial Spondyloarthritis was approved in the EU on 23 July 2012.

JIA was approved in the US on 21 February 2008 for patients 4 years of age and older and in the EU on 25 August 2008 for patients age 13 to 17 years. JIA was approved in Australia on 15 July 2009 for patients 4 to 17 years of age. JIA was approved in Canada on 28 November 2012 for patients 4 to 17 years of age. On 18 March 2011, JIA was approved in the EU for patients 4 to 12 years of age. On 25 February 2013, JIA was approved in the EU for patients 2 to < 4 years of age. On 22 November 2012, Pediatric Crohn's disease was approved in the EU for patients 6 to 17 years of age.

Has been changed to read:

Humira was first approved for the treatment of patients with RA in the US in December 2002 and in the EU in September 2003. In addition, adalimumab is approved for the treatment of patients with polyarticular JIA (2 years of age and older), early RA, PsA, ankylosing spondylitis (AS), Crohn's disease (CD) (adult and pediatric), ulcerative colitis (UC), plaque psoriasis (plaque Ps) (adult), and hidradenitis suppurativa (HS) in the EU, US, and the rest of the world. Adalimumab is also approved for the treatment of patients with pediatric ERA, pediatric plaque Ps, and non-radiographic axial spondyloarthritis (nr-axSpA) in the EU and several other countries, as well as for intestinal Behçet's disease (BD) in Japan, Argentina, Korea, and Taiwan. As of 31 December 2015, Humira has been approved for at least one indication in over 90 countries worldwide (polyarticular JIA is approved in over 80 countries).

Section 4.0 Rationale
First paragraph previously read:

Humira is approved in the US for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 4 years of age and older. Humira can be used alone or in combination with methotrexate.

Has been changed to read:

Humira is approved in the US for reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older. Humira can be used alone or in combination with methotrexate (MTX).

Section 4.0 Rationale
Second paragraph, first sentence previously read:

In the EU, Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients aged 2 to 17 years who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Has been changed to read:

In the EU, Humira in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in patients 2 years of age and older who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Section 4.0 Rationale
Last paragraph previously read:

Patients who consent to participate in the registry, will be followed for up to 10 years following enrollment in the Humira treatment arm, providing long-term safety and effectiveness data on Humira in moderately to severely active polyarticular or polyarticular-course JIA patients.

Has been changed to read:

Patients who consent to participate in the registry, will be followed for up to 10 years starting from Day 1 in the registry arm, providing long-term safety data for 10 years and long-term effectiveness data for 5 years. For the patients in the HUMIRA registry arm

after having been initially in the MTX registry arm, the 10 year follow-up will restart from Day 1 in the HUMIRA registry arm.

Section 6.0 Investigational Plan
First paragraph, fifth and sixth sentence previously read:

Starting at Year 6, patients will be followed annually for SAEs, congestive heart failure (CHF), pregnancies and malignancies through Year 10. For JIA patients 2 to< 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry, emergent AESI, SAEs and pregnancy (at the age when a patient can become pregnant) will be collected for the full 10 years.

Has been changed to read:

Starting at Year 6, patients will be followed annually for SAEs, a subset of AESI that includes congestive heart failure (CHF), malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies through Year 10. For polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry, SAEs, all AESI, and pregnancy (at the age when a patient can become pregnant) will be collected for the full 10 years.

Section 6.1 Selection of Population
Delete: second bullet

Patients in the JIA registry in the U.S. may also be co-enrolled in the AbbVie sponsored Humira pediatric injection site pain study which includes a new formulation of adalimumab. Collection of safety information for patients that are co-enrolled in the JIA registry and the AbbVie Humira pediatric injection site pain study are described in Section 6.6.5.

Section 6.5 Registry Duration
Delete: second paragraph

During the first 5 years of the registry, all available patient data, as defined by the protocol, will be collected at each doctor's visit. Starting at Year 6 of the registry, patient data will be collected annually for congestive heart failure (CHF), malignancies, SAEs, and pregnancies through Year 10 (Figure 1). JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry will have AESI, SAEs, and pregnancy (potentially at the age when patient can become pregnant) collected for the full 10 years as defined by the protocol (Figure 2).

Section 6.5 Registry Duration
Fifth paragraph
Delete: first sentence

Patients who develop an Adverse Event of Special Interest (AESI) or SAE while in the registry will be followed throughout the patient's participation in the registry or direct to HCP follow-up process until satisfactory resolution or until 70 days following the last registry dose (whichever is longer).

Section 6.5 Registry Duration
Sixth paragraph
Delete: third, fourth, fifth, sixth, seventh, and eighth sentence

Safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The first questionnaire will capture data from the date the patient discontinued the registry through one year prior to the start date of collection of data for the second questionnaire. The questionnaire to be used through Year 5 focuses on the collection of Adverse Events of Special Interest (AESI), hospitalizations, surgeries, and death. The questionnaire to be used for Years 6 through 10 focuses on collection of congestive heart failure, malignancies, hospitalizations, surgeries, and death (Figure 1). JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry will have AESI, hospitalizations, surgeries and death collected for the full 10 years as defined by the protocol (Figure 2). The

questionnaire may be completed by the registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician).

Section 6.6 Registry Conduct
Fifth and sixth paragraph previously read:

At the completion of Year 5 (Month 60), patients data will be collected annually for congestive heart failure and malignancies, SAEs and pregnancies through Year 10 of registry participation as indicated in the registry schematic (Figure 1).

For JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry will have AESI, SAEs, and pregnancy (during the study potentially at the age when patient can become pregnant) will be collected for full 10 years as defined by the protocol (Figure 2).

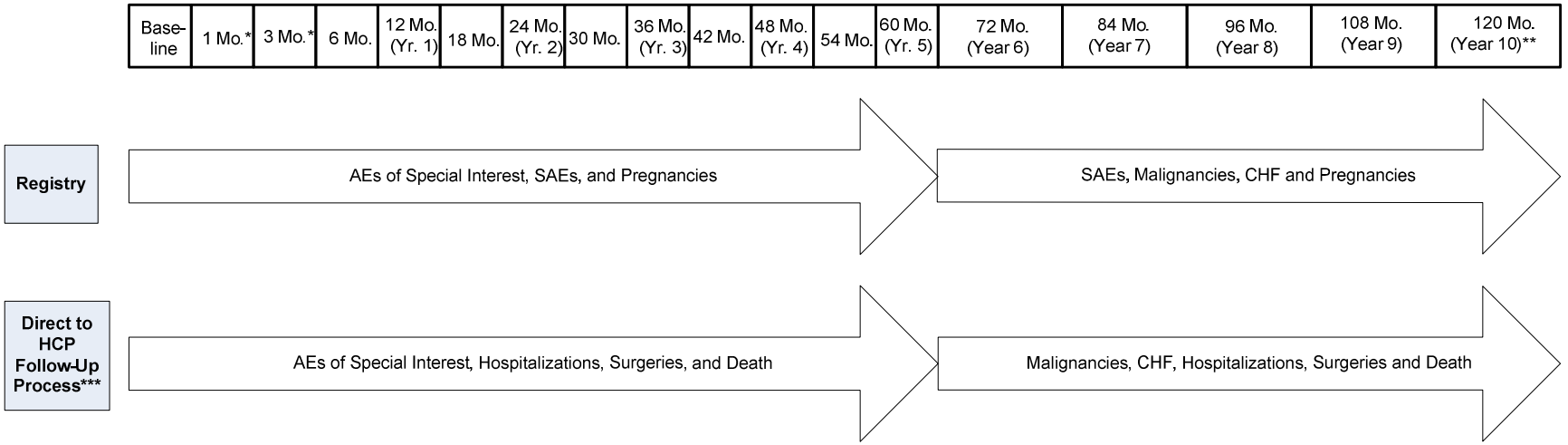
Has been changed to read:

For collection of Safety data, see Figure 1 and Figure 2.

Figure 1. Registry Schematic for JIA Patents 4 to 17 Years of Age
Previously read:

Figure 1. Registry Schematic for JIA Patents 4 to 17 Years of Age

With Humira, eow or Methotrexate (as directed)



eow = every other week

* For patients not rolling over from Study DE038 or Study M10-444.

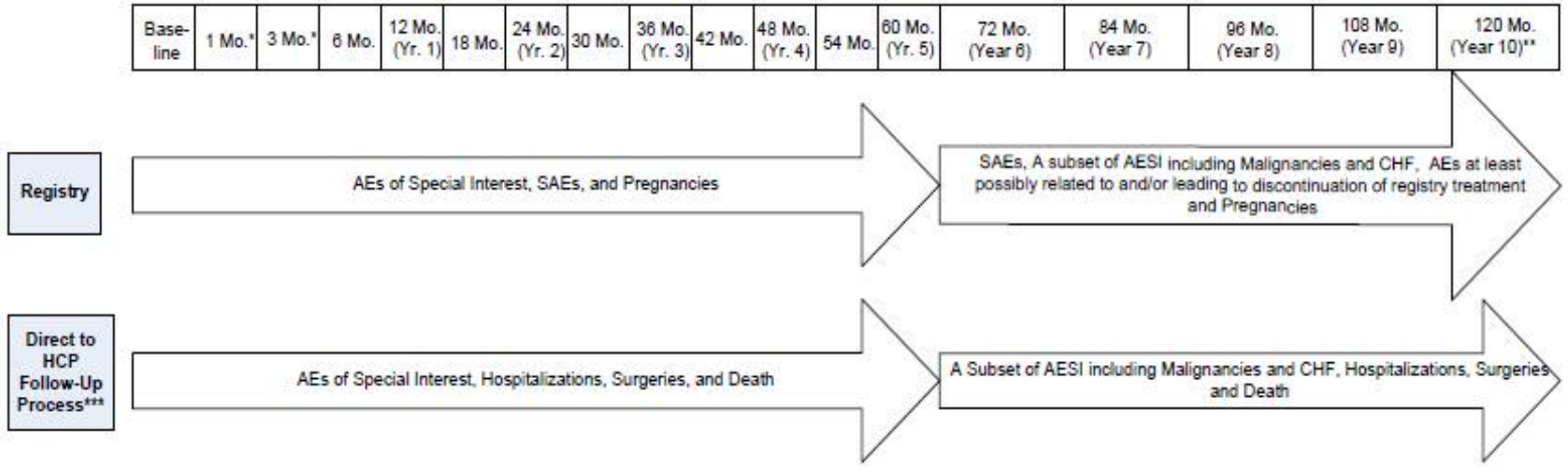
** Participation in the registry may be longer if patient switches from MTX arm to Humira arm.

*** The Direct to HCP Follow-up Process will collect events annually.

Has been changed to read:

Figure 1. Registry Schematic for Polyarticular JIA Patients 4 to 17 Years of Age

With HUMIRA®, eow or Methotrexate (as directed)



eow = every other week

* For patients not rolling over from Study DE038 or Study M10-444.

** Participation in the registry may be longer if patient switches from MTX arm to Humira arm.

*** The Direct to HCP Follow-up Process will collect events annually.

Table 1. Registry Activities
Table note "f."
Second, third and fourth sentence previously read:

From Year 6 through Year 10 SAEs, malignancies, CHF and pregnancies will be collected. For subjects that participate in the direct to HCP follow-up process AESI, hospitalizations, surgeries, and death will be collected from Year 1 through Year 5 and malignancies, CHF, hospitalizations, surgeries and death will be collected from Year 6 to Year 10. For JIA patients from 2 to < 4 years of age while in the registry AESI, SAEs and pregnancies will be collected through Year 10 and those who participate in the direct to HCP follow-up process will have AESI, hospitalizations, surgeries and death collected annually through Year 10.

Has been changed to read:

From Year 6 through Year 10 SAEs, a subset of AESI that includes congestive heart failure (CHF), malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment and pregnancies will be collected. For patients that participate in the direct to HCP follow-up process AESI, hospitalizations, surgeries, and death will be collected annually from Year 1 through Year 5 and malignancies, CHF, hospitalizations, surgeries and death will be collected annually from Year 6 to Year 10. For polyarticular JIA patients from 2 to < 4 years of age while in the registry AESI, SAEs and pregnancies will be collected through Year 10 and those who participate in the direct to HCP follow-up process will have AESI, hospitalizations, surgeries and death collected annually through Year 10.

Table 1. Registry Activities
Table note "h."
First sentence previously read:

Patients who develop an Adverse Event of Special Interest (AESI) or SAE while in the registry will be followed throughout the patient's participation in the registry or direct to HCP follow-up process until satisfactory resolution or until 70 days following the last registry dose (whichever is longer).

Has been changed to read:

Patients who develop an Adverse Event of Special Interest (AESI) or SAE while in the registry will be followed throughout the patient's participation in the registry or direct to HCP follow-up process until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

Section 6.6.3 Vitals, Growth Assessments and Tanner Staging
First and second sentence previously read:

Vitals including blood pressure, pulse, temperature, will be recorded at Baseline and at each visit. Growth assessments, including height and weight, will be recorded at Baseline and each visit and Tanner Maturation Staging (Appendix H) will be recorded at Baseline and every 12 months thereafter through Year 5.

Has been changed to read:

Vitals including blood pressure, pulse, temperature, will be recorded at Baseline and at each visit through Year 5. Growth assessments, including height and weight, will be recorded at Baseline and at each visit through Year 5 and Tanner Maturation Staging (Appendix H) will be recorded at Baseline and every 12 months thereafter through Year 5.

Section 6.6.4 Prior and Concomitant Medications
Last paragraph previously read:

During registry participation, patients should not be enrolled into any interventional clinical trials except for the AbbVie sponsored Humira pediatric injection site pain study (conducted in the U.S. only) which includes a new formulation of adalimumab. Collection of safety information for patients that are co-enrolled in the JIA registry and the AbbVie Humira pediatric injection site pain study are described in Section 6.6.5.

Has been changed to read:

During registry participation, patients should not be enrolled into any interventional clinical trials.

Section 6.6.5 Safety Data Collection
Second paragraph previously read:

For JIA registry patients that are co-enrolled in the AbbVie sponsored Humira pediatric injection site pain study, all safety information including AESI (as listed in Section 7.1.2) and SAEs with onset during their participation in the injection site pain study will be captured only in the injection site pain study to avoid duplication. The event(s) which occur during the AbbVie sponsored Humira pediatric injection site pain study will be followed and documented until satisfactory resolution within the pediatric injection site pain study. AbbVie will report the safety information as per protocol for the JIA registry as derived from the safety information collected during co-enrollment in the AbbVie Humira pediatric injection site pain study.

Has been changed to read:

During the first 5 years of the registry, all available patient data, including SAEs, AESI as defined by the protocol and pregnancies will be collected at each doctor's visit. However, SAEs, AESI and pregnancy information can be collected at any time during the registry, not only at each doctor's visit. During Years 6 through 10 of the registry, patient data will be collected annually, including SAEs, a subset of AESI that includes congestive heart failure, malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies (Figure 1). Polyarticular JIA patients 2 to < 4 years of age, in countries with available local approval for this group of patients at the time of consent to the registry, will have SAEs, AESI, and pregnancy (potentially at the age when patient can become pregnant) collected for the full 10 years as defined by the protocol (Figure 2). Patients who develop an SAE or Adverse Events of Special Interest (AESI) while in the registry will be followed throughout the patient's participation in the registry until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

For patients participating in the HCP process, safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire to be used through Year 5 focuses on the collection of Adverse Events of Special Interest

(AESI), hospitalizations, surgeries, and death. The questionnaire to be used for Years 6 through 10 focuses on collection of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group, will have AESI, hospitalizations, surgeries and death collected for the full 10 years as defined by the protocol (Figure 2). The questionnaire may be completed by the registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician).

Section 6.6.5 Safety Data Collection
Third paragraph previously read:

All patients who participate in or discontinue from the registry during the first 5 years will be followed for SAEs and AEs of Special Interest until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the registry during Years 6 through 10, will be followed for all SAEs, CHF and malignancies until satisfactory resolution or for 70 days after last dose of registry drug (whichever is longer) to evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up through Year 5 will be followed for AESI, hospitalizations, surgeries and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up during Registry Year 6 through Year 10 will be followed for malignancies, CHF, hospitalizations, surgeries, and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 1).

Has been changed to read:

All patients who participate in or discontinue from the registry during the first 5 years will be followed for SAEs and AEs of Special Interest until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the registry during Years 6

through 10, will be followed for all SAEs, CHF and malignancies until satisfactory conclusion or for 70 days after last dose of registry drug (whichever is longer) to evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up through Year 5 will be followed for AESI, hospitalizations, surgeries and death until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up during Registry Year 6 through Year 10 will be followed for malignancies, CHF, hospitalizations, surgeries, and death until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 1).

Section 6.6.5 Safety Data Collection
Fourth paragraph previously read:

All polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry who participate in or discontinue from the Registry up through Year 10 will be followed for AESI and SAEs until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All polyarticular JIA patients 2 to < 4 years of age who participate in or discontinue from the direct to HCP follow-up process up through Registry Year 10 will be followed for AESI, hospitalizations, surgeries and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 2).

Has been changed to read:

All polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry who participate in or discontinue from the Registry up through Year 10 will be followed for AESI and SAEs until satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All polyarticular JIA patients 2 to < 4 years of age who participate in or discontinue from the direct to HCP follow-up process up through Registry Year 10 will be followed for AESI, hospitalizations, surgeries and death until

satisfactory conclusion or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 2).

Section 6.6.6 Physician Global Assessment and Patient Reported Outcome Measurements
First paragraph, fourth and fifth sentence previously read:

The following clinical assessments will be used: physical function of the Disability Index of Childhood Health Assessment Questionnaire (DICHAQ), (Appendix E) and Parent's Global Assessment of patient's pain and overall well-being (VAS) (Appendix F). Effectiveness of therapy provided by the physician will be collected through the Physician's Global Assessments (Appendix F), Joint Assessments (Appendix D) and available CRP or ESR values beginning with the enrollment visit, Months 1 and 3 (if applicable) and 6 months and every 6 months thereafter through Year 5.

Has been changed to read:

The following clinical assessments will be used: physical function of the Disability Index of Childhood Health Assessment Questionnaire (DICHAQ), and Parent's Global Assessment of Patient's Disease Activity (VAS) and Parent's Assessment of patient's pain (VAS). Effectiveness of therapy provided by the physician will be collected through the Physician's Global Assessment of Disease Activity (VAS).

Section 6.6.7 Joint Assessment
Previously read:

A thirty-nine joint assessment will be recorded at all registry visits starting at the enrollment visit to assess the number of active joints.

Has been changed to read:

A thirty-nine joint assessment (Appendix D) will be recorded starting at the enrollment visit and at each registry visit thereafter through Year 5 to assess the number of active joints.

Section 6.6.9 Inactive Disease Assessment
First paragraph previously read:

The inactive disease assessment will be recorded at all registry visits starting at the enrollment visit. A patient has inactive disease if he/she meets the following:

Has been changed to read:

The inactive disease assessment will be recorded starting at the enrollment visit and at each registry visit thereafter through Year 5. A patient has inactive disease if he/she meets the following:

Section 6.7.1 Effectiveness Variables
Second paragraph, first sentence previously read:

The effectiveness of therapy evaluation provided by the patient will be collected with clinical assessments as discussed in Section 6.6.6.

Has been changed to read:

The effectiveness of therapy evaluation provided by the patient or parent will be collected with clinical assessments as discussed in Section 6.6.6.

Section 6.7.1 Effectiveness Variables
Second paragraph, first and second bullet previously read:

- Parent's Global Assessment of patient's pain (VAS)
- Parent's Global Assessment of overall well-being (VAS)

Has been changed to read:

- Parent's Assessment of Patient's Pain (VAS)
- Parent's Global Assessment of Patient's Disease Activity (VAS)

Section 6.7.1 Effectiveness Variables
Third paragraph, fourth and fifth bullet previously read:

- Number of joints with limit of motion LOM
- Number of joints with pain of passive motion (POM)

Has been changed to read:

- Number of joints with limitation of passive motion (LOM)
- Number of joints with pain on passive motion (POM)

Section 6.7.2 Safety Variables
Second paragraph previously read:

SAEs and Adverse Events of Special Interest (AESI) will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent/patient authorization) throughout the registry or Direct to HCP follow-up process until satisfactory resolution or until 70 days following last dose of registry drug (whichever is longer). In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest (AESI) will be collected throughout the interruption. If a patient switches from MTX to Humira treatment, SAEs and AEs of Special Interest will continue to be collected under the Humira arm. If treatment with Humira or MTX is permanently discontinued for any reason, patients will be discontinued from treatment and the reason for discontinuation will be recorded. Patients that discontinue treatment will be encouraged to remain in the registry and will be followed for safety and effectiveness through Year 5 and SAEs and AESI will be followed until satisfactory resolution or until 70 days following last dose of registry drug (whichever is longer), and starting at Year 6, patients will be followed annually for the subset of AESI which include congestive heart failure and malignancies and SAEs through Year 10 of the registry until satisfactory resolution or until 70 days following last dose of registry drug (whichever is longer). For JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry the AESI and SAEs will be collected for the full 10 years as defined by the protocol (Figure 2) and will be followed up until

satisfactory resolution or until 70 days following last dose of registry drug (whichever is longer). Patients that discontinue from the Registry (before 10 years) will be offered to participate in the direct to HCP process as allowed by applicable local regulations. Safety data from these patients will be collected by completion of a simplified HCP questionnaire on an annual basis. The questionnaire focuses on the collection of Adverse Events of Special Interest, hospitalizations, surgeries, death and JIA related medication use through Year 5 and malignancies, CHF, hospitalizations, surgeries and death from Year 6 through Year 10 (Figure 1). JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry and participating in the HCP follow-up process will have AESI, hospitalizations, surgeries, death and JIA related medication use collected for the full 10 years (Figure 2).

Has been changed to read:

SAEs and Adverse Events of Special Interest (AESI) will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent/patient authorization) throughout the registry or Direct to HCP follow-up process until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest (AESI) will be collected throughout the interruption. If a patient switches from MTX to Humira treatment, SAEs and AEs of Special Interest will continue to be collected under the Humira arm. If treatment with Humira or MTX is permanently discontinued for any reason, patients will be discontinued from treatment and the reason for discontinuation will be recorded on the Study Drug Completion eCRF. Patients that discontinue treatment will be encouraged to remain in the registry and will be followed for safety and effectiveness through Year 5 and SAEs and AESI will be followed until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer), and starting at Year 6, patients will be followed annually for the subset of AESI which include congestive heart failure and malignancies and SAEs through Year 10 of the registry until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). For polyarticular

JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry the AESI and SAEs will be collected for the full 10 years as defined by the protocol (Figure 2) and will be followed up until satisfactory conclusion or until 70 days following last dose of registry drug (whichever is longer). Patients that discontinue from the Registry (before 10 years) will be offered to participate in the direct to HCP process as allowed by applicable local regulations. Safety data from these patients will be collected by completion of a simplified HCP questionnaire on an annual basis. The questionnaire focuses on the collection of Adverse Events of Special Interest, hospitalizations, surgeries, death and polyarticular JIA related medication use through Year 5 and malignancies, CHF, hospitalizations, surgeries and death from Year 6 through Year 10 (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry and participating in the HCP follow-up process will have AESI, hospitalizations, surgeries, death and polyarticular JIA related medication use collected for the full 10 years (Figure 2).

Section 6.7.2 Safety Variables
Third, fourth and fifth paragraph previously read:

SAE reports will be completed and submitted using an electronic version of AbbVie's standard SAE form (Section7.0).

Adverse Events of Special Interest (AESI) will be collected on separate data collection forms. These forms will capture specific information relevant to the AESI.

Pregnancy must be reported to AbbVie and will be followed all through out the entirety of the registry (refer to Section 7.6 for details).

Has been changed to read:

SAEs, Adverse Events of Special Interest (AESI), and pregnancies will be collected on their respective eCRFs (refer to Section 7.0 and Section 7.1.9 for details).

Section 7.0 through 7.6
Section number and title previously read:

7.0 Adverse Events/Adverse Events of Special Interest Reporting

7.1 Definitions

7.1.1 Adverse Event

7.1.2 Adverse Event of Special Interest

7.1.3 Serious Adverse Events

7.2 Adverse Event Severity

7.3 Relationship to Pharmaceutical Product

7.4 Adverse Event Collection Period

7.5 Serious Adverse Event Reporting

7.6 Pregnancy

Has been changed to read:

7.0 Complaints

7.1 Medical Complaints

7.1.1 Adverse Events

7.1.2 Adverse Event Definition

7.1.3 Adverse Events of Special Interest

7.1.4 Serious Adverse Events

7.1.5 Adverse Event Severity

7.1.6 Relationship to Pharmaceutical Product

7.1.7 Adverse Event Collection Period

7.1.8 Serious Adverse Event Reporting

7.1.9 Pregnancy

Section 7.0 Adverse Events/Adverse Events of Special Interest Reporting
Previously read:

7.0 Adverse Events/Adverse Events of Special Interest Reporting

The Physician will monitor each patient from the time the applicable registry-specific parental informed consent/patient assent form (authorization form) is signed through Registry Year 5 for SAEs and Adverse Events of Special Interest (AESI) until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. The Physician will monitor each patient from Year 6 through Year 10 for SAEs, malignancies and CHF from the time the applicable registry-specific parental informed consent/patient assent form (authorization form) is signed. The Physician will monitor all patients who participate in or discontinue from the direct to HCP follow-up process up through Year 5 for AESI, hospitalizations, surgeries and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. The Physician will monitor all patients who participate in or discontinue from the direct to HCP follow-up process up during Registry Year 6 through Year 10 for malignancies, CHF, hospitalizations, surgeries, and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 1).

The Physician will monitor all JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry who participate in or discontinue from the Registry up through Year 10 for AESI and SAEs. The Physician will monitor all JIA patients 2 to < 4 years of age who participate in or discontinue from the direct to HCP follow-up process up through Registry Year 10 for AESI, hospitalizations, surgeries and deaths until satisfactory resolution or for 70 days

after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 2).

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.2.

The Physician will assess and record the AE in detail including the date of onset, signs/symptoms, severity, time course, duration and outcome, relationship of the AE to treatment, an event diagnosis, if known, and any action(s) taken. For SAEs considered "possibly related," "probably not related" "and not related" to the registry treatment, the Physician will provide another cause of the event. For AEs to be considered sporadic, the events must be of similar nature and severity. SAEs or Adverse Events of Special Interest, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. Information about medications taken for the SAE or the Adverse Event Special Interest will be collected.

All SAEs and Adverse Event of Special Interest will be followed to a satisfactory conclusion.

Has been changed to read:

7.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The Sponsor's product in this registry contains both:

- Biologic compound(s) and

- Device component(s) (pre-filled syringe, pen).

Complaints associated with any component of the Sponsor's product must be reported to the Sponsor. For adverse events, please refer to Sections 7.1 through 7.1.8. For product complaints, please refer to Section 7.2.

7.1 Medical Complaints

7.1.1 Adverse Events

Adverse Events/Adverse Events of Special Interest Reporting:

The Physician will monitor each patient from the time the applicable registry-specific parental informed consent/patient assent form (authorization form) is signed throughout the Registry participation for all Adverse Events as described in Section 6.6.5 (Safety Data Collection).

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.3.

The Physician will assess and record the AE in detail including the date of onset, signs/symptoms, severity, time course, duration and outcome, relationship of the AE to treatment, an event diagnosis, if known, and any action(s) taken. For SAEs considered "possibly related," "probably not related" "and not related" to the registry treatment, the Physician will provide another cause of the event. For AEs to be considered sporadic, the events must be of similar nature and severity. SAEs or Adverse Events of Special Interest, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. Information about medications taken for the SAE or the Adverse Event Special Interest will be collected.

All events reported throughout the patient's participation in the registry will be followed until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

Section 7.4 Adverse Event Collection Period
Previously read:

Adverse Events of Special Interest will be reported any time after the last dose MTX or Humira if the Physician believes the event is related to MTX or Humira treatment. In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest will be collected throughout the interruption. If treatment with MTX or Humira is permanently discontinued for any reason, the reason will be recorded, and the patient will be encouraged to remain in the registry. For patients enrolled from the prior juvenile idiopathic arthritis (JIA) Humira study, ongoing AEs will be collected within the primary clinical trial and will be captured as part of the patient's medical history in the registry.

All patients who participate in or discontinue from the registry during the first 5 years will be followed for SAEs and AEs of Special Interest until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the registry during Years 6 through 10, will be followed for all SAEs, CHF and malignancies until satisfactory resolution or for 70 days after last dose of registry drug (whichever is longer) to evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process up through Year 5 will be followed for AESI, hospitalizations, surgeries and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety. All patients who participate in or discontinue from the direct to HCP follow-up process during Registry Year 6 through Year 10 will be followed for malignancies, CHF, hospitalizations, surgeries, and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 1).

All JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry who participate in or discontinue from the Registry up through Year 10 will be followed for AESI and SAEs. All JIA patients 2 to < 4 years of age who participate in or discontinue from the direct to HCP follow-up process up through Registry Year 10 will be followed for AESI, hospitalizations, surgeries and death until satisfactory resolution or for 70 days after their last dose of registry drug (whichever is longer) to further evaluate safety (Figure 2).

The Follow-up received on any ongoing SAEs and/or AESI post registry conclusion should be reported using standard Post Marketing Spontaneous Reporting.

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.2.

Has been changed to read:

Adverse Events of Special Interest will be reported any time after the last dose MTX or Humira if the Physician believes the event is related to MTX or Humira treatment. In the event Humira therapy is interrupted, SAEs and Adverse Events of Special Interest will be collected throughout the interruption. If treatment with MTX or Humira is permanently discontinued for any reason, the reason will be recorded, and the patient will be encouraged to remain in the registry. For patients enrolled from the prior polyarticular juvenile idiopathic arthritis (JIA) Humira study, ongoing AEs will be collected within the primary clinical trial and will be captured as part of the patient's medical history in the registry.

During the first 5 years of the registry, all available patient data, including SAEs, AESI as defined by the protocol and pregnancies will be collected at each doctor's visit. However, SAEs, AESI and pregnancies can be collected at any time, not only at each doctor's visit. During Years 6 through 10 of the registry, patient data to be collected annually, including

SAEs, a subset of AESI that includes congestive heart failure, malignancies, AEs at least possibly related to and/or leading to discontinuation of registry treatment, and pregnancies (Figure 1). Polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group of patients at the time of consent to the registry will have SAEs, AESI, and pregnancy (potentially at the age when patient can become pregnant) collected for the full 10 years as defined by the protocol (Figure 2). Patients who develop an SAE or Adverse Event of Special Interest (AESI) while in the registry will be followed throughout the patient's participation in the registry until satisfactory conclusion or until 70 days following the last registry dose (whichever is longer).

For patients participating in the HCP process, safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire to be used through Year 5 focuses on the collection of Adverse Events of Special Interest (AESI), hospitalizations, surgeries, and death. The questionnaire to be used for Years 6 through 10 focuses on collection of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death (Figure 1). In addition, for polyarticular JIA patients 2 to < 4 years of age in countries with available local approval for this group, Safety data will be collected by the participating HCP using the HCP questionnaire on an annual basis. The questionnaire will focus on collection of AESI, hospitalizations, surgeries, and death and will be collected for the full 10 years as defined by the protocol (Figure 2). The questionnaire may be completed by the registry physician or the patient's current HCP (if the patient is no longer under the care of a registry physician).

The Follow-up received on any ongoing SAEs and/or AESI post registry conclusion should be reported using standard Post Marketing Spontaneous Reporting.

Follow-up contact can include a certified letter or phone call to the patient. All contact must be clearly documented in the patient's registry file.

All medications used to treat these events will also be captured. A complete list of the Adverse Events of Special Interest can be found in Section 7.1.3.

Section 7.5 Serious Adverse Event Reporting
Previously read:

In the event of a SAE, and additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to registry drug or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event or nonserious event of malignancy in patients 30 years of age and younger into the electronic data capture (EDC) system. Serious adverse events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the EDC system or if the EDC is system is not operable should be reported on the SAE Non-CRF paper forms and faxed to the AbbVie Immunology Clinical Safety Management Team within 24 hours of being made aware of the adverse event.

FAX to: [redacted]

For SAE concerns, contact the Immunology Safety Team at:

[redacted]

For any subject safety concerns, please contact the physician listed below:

Has been changed to read:

In the event of a SAE, and additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to registry drug or not, the physician will notify the AbbVie Clinical Pharmacovigilance Team within 24 hours of the physician becoming aware of the event by entering the Serious Adverse Event or nonserious event of malignancy in patients 30 years of age and younger into the electronic data capture (EDC) system. Serious Adverse Events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the EDC system or if the EDC is not operable should be documented on the SAE Non-CRF paper forms and emailed to AbbVie Clinical Pharmacovigilance or faxed to AbbVie Clinical Pharmacovigilance within 24 hours of being made aware of the Serious Adverse Event.

For SAE concerns, contact the Immunology Safety Team at:

For any subject safety concerns, please contact the Primary Study Designated Physician listed below:

Should in case of subject safety concerns or medical emergencies the Primary Study Designated Physician be unavailable, please call the following central back-up number:

Phone: 

Section 7.6 Pregnancy
Previously read:

Pregnancy must be reported to AbbVie (see contact details in Section 7.5) within 1 working day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected. Pregnancies will be collected from the date of the first dose through 150 days following the last dose of registry dose. Physicians should refer to their local prescribing information when making treatment decisions for patients who become pregnant while being treated with Humira (monotherapy or combination therapy with MTX) or MTX (monotherapy without Humira). Patients who become pregnant and interrupt Humira or MTX treatment should remain in the registry and should continue to be monitored for new SAEs and Adverse Events of Special Interest. Patients who become pregnant and interrupt their Humira therapy may remain in the registry provided they restart Humira therapy within 15 months of their last dose.

Pregnancy in a registry patient is not considered an AE. However the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Has been changed to read:

Pregnancy in a registry patient must be reported to AbbVie (see contact details in Section 7.1.8) within 1 working day of the site becoming aware of the pregnancy. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected. Pregnancies will be collected from the date of the patient's first dose of registry drug through 150 days following the last dose or the end of the patient's participation in the registry (whichever is longer).

Pregnancy in a registry patient is not considered an AE. However the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Section 7.2 Product Complaint
Add: new section and text, renumber subsequent sections

7.2 Product Complaint

7.2.1 Definition

A Product Complaint is any Complaint (see Section 7.0 for the definition) related to the biologic or drug component of the product or to the medical device component.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

7.2.2 Reporting

Product Complaints concerning the product and/or device must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (syringe, pen, etc.). In instances where a return is requested, every effort should

be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

Product complaints involving a non-Sponsor drug, device or combination product, under study, should be reported to the identified contact or appropriate manufacturer, as necessary per local regulations.

Section 7.7 Data Collection Procedures for Patients Who Participate in the Direct to HCP Process
First paragraph, first and second sentence previously read:

For patients participating in the direct to HCP process, HCPs will document any hospitalizations or surgeries, any Adverse Event of Special Interest and death as defined in Section 7.1.2 annually via a paper questionnaire or eCRF through the first 5 years of the patient's enrollment date in the registry. HCPs will document any occurrence of hospitalizations, surgeries, death, malignancies, and CHF annually via a questionnaire or eCRF beginning at Year 6 through Year 10.

Has been changed to read:

For patients participating in the direct to HCP process, HCPs will document any Adverse Event of Special Interest, hospitalizations, surgeries, and death as defined in Section 7.1.3 annually via a paper questionnaire or eCRF through the first 5 years of the patient's enrollment date in the registry. HCPs will document any occurrence of a subset of AESI that includes congestive heart failure and malignancies, hospitalizations, surgeries, and death annually via a questionnaire or eCRF beginning at Year 6 through Year 10.

Section 8.1 Quality Assurance
Fifth paragraph previously read:

Monitoring visits will be performed at a subset of the sites. At the visits a quality assurance check will be performed against entries on the paper and eCRF and a quality assurance check will be performed to ensure that the Physician is complying with the protocol and regulations. The monitoring plan will detail how sites will be selected for the monitoring visits and what data will be source data verified during the visit. Throughout the registry, UBC and AbbVie will periodically follow up with the sites to ensure that SAEs and Adverse Events of Special Interest are being reported.

Has been changed to read:

At least one monitoring visit will be performed at each site for the duration of the registry. During the monitoring visit entries on the eCRF are reviewed against source documents to verify accuracy and appropriate completion of the eCRF. The monitoring plan will detail how sites will be selected for the monitoring visits and what data will be source data verified during the visit. Throughout the registry, UBC and AbbVie (if needed) will periodically follow-up with the sites to ensure that SAEs and Adverse Events of Special Interest are being reported.

Section 8.1 Quality Assurance
Sixth paragraph, fourth sentence previously read:

All other paper questionnaires (e.g., direct to HCP questionnaire) will be entered into the database.

Has been changed to read:

All other paper questionnaires (e.g., direct to HCP questionnaire) will be reviewed for completion by the site or the CRO (as appropriate) prior to being entered into the database.

Section 9.0 Case Report Forms and Source Documents
Fourth paragraph, last sentence previously read:

Patient completed questionnaires (DICHAQ, CHQ-PF50), parent global assessment of child's well being (VAS), pain assessment (VAS), physician global assessment of child's well being (VAS) and joint assessments will be documented on a paper Case Report Form, which will be sent to UBC for data entry.

Has been changed to read:

Patient completed questionnaires (DICHAQ, CHQ-PF50); parent's global assessment of patient's disease activity (VAS), parent's assessment of patient's pain (VAS), physician's global assessment of disease activity (VAS) and joint assessments will be documented on a paper Case Report Form, which will be sent to UBC for data entry.

Section 10.2 Demographics and Registry Enrollment Characteristics
Last bullet
Last sub-bullet previously read:

(Humira arm) = last Humira dose date in the registry – first recorded Humira dose (initial dose) + 14 – total days of any treatment interruptions.

Has been changed to read:

(Humira arm) = last Humira dose date in the registry – first recorded Humira dose (initial dose) + 14 – total days of any treatment interruptions. For patients who rolled over from Study DE038 and were in the Placebo arm during the double-blind period of this study, the duration of the double-blind period will be subtracted from total exposure.

Section 10.3 Safety Analysis
Second and third bullet previously read:

- Registry Treatment-Emergent AEs: SAEs and AEs of Special Interest occurring from the first dose in the registry through the last dose plus 70 days in the registry, excluding AEs occurring during TI which are more than 70 days after the last dose of registry drug prior to the TI.

- All Treatment Emergent AEs: SAEs and AEs of Special Interest occurring from the first recorded dose of MTX or Humira through the last dose plus 70 days in the registry, excluding AEs occurring during TI period. For patients enrolled from Study M10-444 and Study DE038, the total number of SAEs and AEs of Special Interest will include the events reported after the first recorded dose of study drug in previous study, any events reported by retrospective data collection, and events reported during this registry.

Has been changed to read:

- Registry Treatment-Emergent AEs: SAEs and AEs of Special Interest occurring from the first dose in the registry through the last dose plus 70 days in the registry, excluding AEs occurring during TI period.
- All Treatment Emergent AEs: SAEs and AEs of Special Interest occurring from the first recorded dose (initial dose) of MTX or Humira through the last dose plus 70 days in the registry, excluding AEs occurring during TI period. For patients enrolled from Study M10-444 and Study DE038, the total number of SAEs and AEs of Special Interest will include the events reported after the first recorded dose of study drug in previous study, except those which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period, any events reported by retrospective data collection, and events reported during this registry.

Section 10.3.1 Analysis of Observational SAEs and AEs of Special Interest
First paragraph, second sentence previously read:

Rates (event per 100 patient year of observation) of SAEs and AEs of Special Interest will be provided.

Has been changed to read:

Rates (event per 100 patient year of observation) of SAEs and AEs of Special Interest and the 95% confidence interval will be provided.

Section 10.3.1 Analysis of Observational SAEs and AEs of Special Interest
Last paragraph previously read:

The summaries will be provided using data from the first dose in through the last contact irrespective of drug treatment duration.

Has been changed to read:

The summaries will be provided using data from the first day in registry through the last contact irrespective of drug treatment duration.

Section 10.3.2 Analysis of Registry Treatment-Emergent SAEs and AEs of Special Interest
Second paragraph, first sentence previously read:

Registry Treatment-emergent AEs includes AEs occurring from the first dose day of the registry to 70 days after the last dose of registry drug excluding AEs occurring during TI which are more than 70 days after the last dose of registry drug prior to the TI.

Has been changed to read:

Registry Treatment-emergent AEs includes AEs occurring from the first dose day of the registry to 70 days after the last dose of registry drug excluding AEs occurring during TI period.

Section 10.3.3 Analysis of All Treatment-Emergent SAEs and AEs of Special Interest
First paragraph, first sentence previously read:

All Treatment-emergent SAEs and AEs of Special Interest includes events occurring after the first recorded dose of MTX or Humira (after the first recorded dose of study drug in previous study for subjects who rollover from Study DE038 or Study M10-444 into this registry), up to 70 days after the last dose of registry drug (excluding SAEs and AEs of Special Interest occurring during TI which are more than 70 days after the last dose of registry drug prior to TI).

Has been changed to read:

All Treatment-emergent SAEs and AEs of Special Interest includes events occurring after the first recorded (initial) dose of MTX or Humira (after the first recorded dose of study drug in previous study for subjects who rollover from Study DE038 or Study M10-444 into this registry), up to 70 days after the last dose of registry drug (excluding SAEs and AEs of Special Interest occurring during TI period and AEs which occurred during the double-blind period in Study DE038 if the patient was in the Placebo arm during this period).

Section 10.4.1 Juvenile Idiopathic Arthritis Core Set of Variables
Item list previously read:

a. Physician's global assessment of patient's disease severity by visual analog scale (VAS) (100 mm VAS, 0 = very good and 100 = very bad)
a. Parent's global assessment of patient's overall well-being by VAS (100 mm VAS, 0 = very good and 100 = very bad)
b. Number of active joints (joints with swelling not due to deformity or joints with limitation of motion [LOM] and with pain on passive motion, tenderness or both)
c. Number of joints with LOM
d. Disability Index of Childhood Health Assessment Questionnaire (DICHAQ)
e. CRP or ESR if collected and available only when part of the physician's site routine care.

Has been changed to read:

a. Physician's global assessment of patient's disease activity by visual analog scale (VAS) (100 mm VAS, 0 = very good and 100 = very bad)
b. Parent's global assessment of patient's disease activity by VAS (100 mm VAS, 0 = very well and 100 = very bad)
c. Number of active joints (joints with swelling not due to deformity or joints with limitation of passive motion [LOM] and with pain and/or tenderness)

d. Number of joints with LOM
e. Disability Index of Childhood Health Assessment Questionnaire (DICHAQ)
f. CRP or ESR if collected and available only when part of the physician's site routine care.

Section 10.4.1.1 Definition PedACR30 Response
Last paragraph previously read:

Improvement of a core set of variables by ≥ 30% will be defined as a percent change from Baseline less than equal to 30 and worsening of a core set of variables by ≥ 30% will be defined as a percent change from Baseline greater than or equal to 30.

Has been changed to read:

Improvement of a core set of variables by ≥ 30% is defined as a percent change from Baseline less than equal to –30% and worsening of a core set of variables by ≥ 30% is defined as a percent change from Baseline greater than or equal to 30%.

Section 10.4.1.3 Definition of JADAS
Item list previously read:

a. Physician's global assessment of patient's disease severity measured on 0–10 cm VAS
b. Parent's global assessment of patient's overall well-being measured on a 0–10 cm VAS
c. Number of active joints (joints with swelling not due to deformity or joints with limitation of motion [LOM] and with pain on passive motion, tenderness or both)
d. Normalized ESR if collected and available only when part of the physician's site routine care.

Has been changed to read:

a. Physician's global assessment of patient's disease activity measured on 0 – 10 cm VAS
b. Parent's global assessment of patient's disease activity measured on a 0 – 10 cm VAS
c. Number of active joints (joints with swelling not due to deformity or joints with limitation of motion [LOM] and with pain on passive motion, tenderness or both)
d. Normalized ESR or CRP if collected and available only when part of the physician's site routine care.

Section 10.4.1.4 Other Analyses
Third sentence previously read:

For patients being enrolled from Study DE038 or other prior AbbVie clinical study, change from open-label lead-in phase will not be calculated since this response was not collected in Study DE038 or other prior AbbVie clinical study.

Has been changed to read:

For patients being enrolled from AbbVie clinical Study DE038 or Study M10-444, baseline will be defined as the last non-missing observation on or before the date of enrollment in the registry since these assessments were not collected in Study DE038 or not collected in Study M10-444 or not collected in both studies.

Section 10.5 Interim Analyses
Add: new last sentence

Effectiveness analyses may also be included in the Interim Reports as deemed appropriate.

Section 15.0 Reference List
Add: new Reference 15

Kingsbury DJ, Bader-Meunier B, Patel G, et al. Safety, effectiveness, and pharmacokinetics of adalimumab in children with polyarticular juvenile idiopathic arthritis aged 2 to 4 years. Clin Rheumatol. 2014;33(10):1433-41.

Appendix A. List of Abbreviations and Definition of Terms
Subsection Abbreviations
Add: "AESI," "AS," "BD," "ERA," "HS," "nr-axSPA, "POM," "Ps," "PsA," and "UC"

AESI	Adverse Events of Special Interest
AS	Ankylosing Spondylitis
BD	Beçhet's Disease
ERA	Enthesitis-Related Arthritis
HS	Hidradenitis Suppurativa
nr-axSPA	Non-radiographic axial spondyloarthritis
POM	Pain on Passive Motion
Ps	Psoriasis
PsA	Psoriatic Arthritis
UC	Ulcerative Colitis

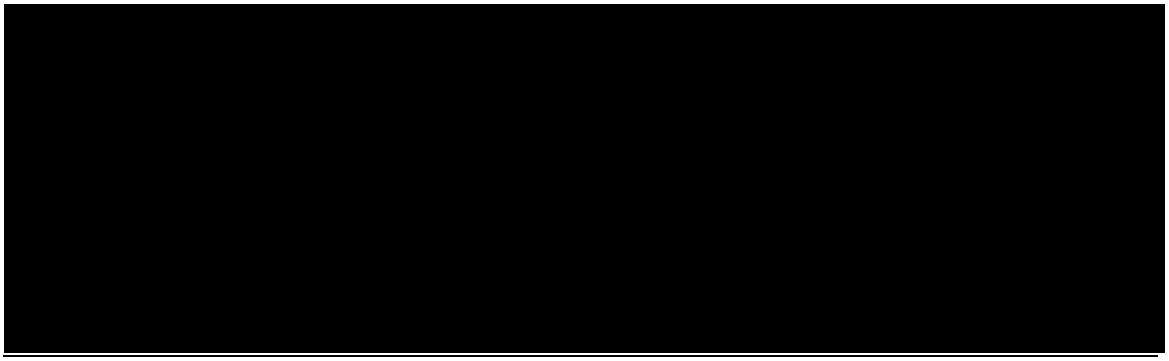
Appendix A. List of Abbreviations and Definition of Terms
Subsection Abbreviations
"LOM" previously read:

LOM Limitation of Motion

Has been changed to read:

LOM Limitation of Passive Motion

Appendix B. List of Protocol Signatories
Previously read:



Has been changed to read:

Document Approval

Study P10262 - A Long-term, Multi-center, Longitudinal Post-marketing, Observational Registry to Assess Long-Term Safety and Effectiveness of HUMIRA (Adalimumab) in Children with Moderately to Severely Active Polyarticular or Polyarticular Course Juvenile Idiopathic Arthritis (JIA) – STRIVE - Amendment 6 - 05Apr2016

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Signed by:	Date:	Meaning Of Signature:
[redacted]		