PERISCOPE

PERI-operative biologic DMARD management: Stoppage or COntinuation during orthoPaEdic operations: The PERISCOPE trial.

Protocol (V1.0 22.02.2023)

ISRCTN: 17691638

IRAS Reference: 321501

Ethics Reference: 23/WS/0049

Co-Chief Investigators: Professor Hemant Pandit and Associate Professor Kulveer Mankia

Leeds Institute of Rheumatic and Musculoskeletal Medicine

Sponsor: University of Leeds

Funder: The National Institute for Health Research Health Technology Assessment Programme (NIHR134800)

This protocol has regard for the HRA guidance and order of content.

Funding acknowledgement and disclaimer: This project is funded by the NIHR Health Technology Assessment (HTA) programme (NIHR134800). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

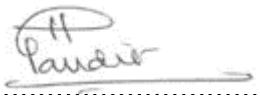
SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

Co-Chief Investigator(s):
Signature: Date: 04/05/2023



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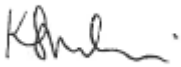

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	Hospital for Special Surgery (HSS), New York.

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1. LIST OF ABBREVIATIONS

Adverse Event	AE
American College of Rheumatology	ACR
Ankylosing Spondylitis	AS
Assessment of SpondyloArthritis international Society Health Index	ASDAS
American Association of Orthopaedic Surgeons	AAOS
Bath Ankylosing Spondylitis Disease Activity Index	BASDAI
Bath Ankylosing Spondylitis Functional Index	BASFI
Biologic Disease-Modifying Anti-Rheumatic Drugs	bDMARDs
Body Surface Area	BSA
British Society for Rheumatology	BSR
British Society for SpondyloArthritis	BRITSpA
Case Report Form	CRF
Chief Investigator	CI
Clinical Disease Activity Index	CDAI
Consolidated Standards of Reporting Trials	CONSORT
C-Reactive Protein	CRP
Data Monitoring and Ethics Committee	DMEC
Data Protection Impact Assessment	DPIA
European Alliance of Associations for Rheumatology	EULAR
European Quality of Life-5 Dimensions – 5 level scale	EQ-5D-5L
General Data Protection Regulations	GDPR

Good Clinical Practice	GCP
Health Assessment Questionnaire Disability Index	HAQ-DI
Health Related Quality of Life	HRQoL
Health Research Authority	HRA
Health Technology Assessment	HTA
Inflammatory Arthritis	IA
Integrated Research Ethics Application System	IRAS
Investigator Site File	ISF
Janus Kinase	JAK
Juvenile Inflammatory Arthritis	JIA
last patient, last visit	LPLV
Methotrexate	MTX
Minimum Clinically Important Difference	MCID
Multidisciplinary team	MDT
Numeric Rating Scale	NRS
Patient Advisory Group	PAG
Patient and Public Involvement	PPI
Patient Information Sheet	PIS
Patient Reported Outcomes Measurement Information System	PROMIS
Patient Reported Outcomes Measurement Information System – Health Assessment Questionnaire	PROMIS-HAQ
Psoriatic Arthritis	PsA
Randomised controlled trial	RCT
Research Ethics Committee	REC
Rheumatoid Arthritis	RA
Serious Adverse Event	SAE
Statistical Analysis Plan	SAP
Surgical site infection	SSI

Trial Management Group	TMG
Trial Steering Committee	TSC
Tumour necrosis factor	TNF
Versus Arthritis	VA
Visual Analogue Scale	VAS
York Trials Unit	YTU

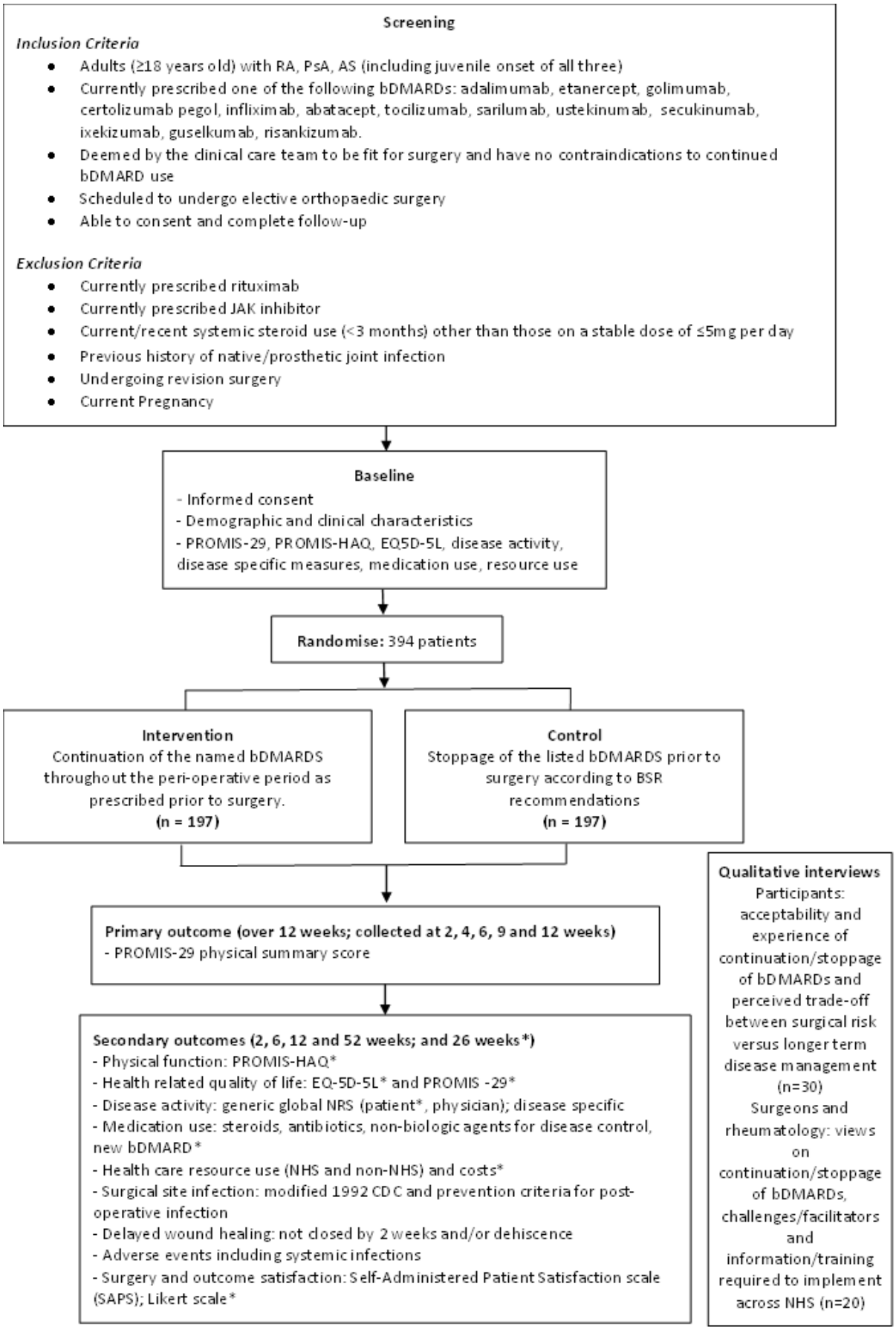
2. TRIAL SUMMARY

Trial Title	PERI-operative biologic DMARD management: Stoppage or COntinuation during orthoPaEdic operations: The PERISCOPE trial.
Short title	PERISCOPE
Clinical Phase	III
Trial Design	Multi-centre, superiority RCT with an internal pilot, economic evaluation and nested qualitative study
Objectives	Objectives: 1. Undertake a 9-month internal pilot to confirm feasibility of the trial. 2. Assess whether continuation of bDMARDs is superior to stoppage with respect to post-operative HRQoL. 3. Investigate the difference between bDMARDs stoppage versus continuation for a range of secondary outcomes, including physical function, HRQoL, disease activity, medication use, health care resource use, surgical outcomes (see below). 4. Conduct a cost-effectiveness analysis. 5. Undertake a qualitative study involving patients, rheumatologists, and surgeons.
Trial Participants	<u>Inclusion criteria:</u> Consenting adults with RA, PsA, AS (including juvenile onset of all three) listed for elective orthopaedic surgery who are currently prescribed the following bDMARDs: TNF inhibitors (adalimumab / etanercept / golimumab / certolizumab pegol / infliximab); CTLA4-Ig (abatacept);

	IL-6 inhibitors (tocilizumab / sarilumab); IL-12/23 inhibitors (ustekinumab); IL-17 inhibitors (secukinumab / ixekizumab); IL-23 p19 inhibitor (guselkumab / risankizumab) deemed by the clinical care team to be fit for surgery and have no contraindications to continued biologic use. <u>Exclusion criteria:</u> Patients currently prescribed JAK inhibitors or rituximab. Current use of systemic steroids (<3 months) other than those on a stable dose of ≤5mg per day. Previous history of native/prosthetic joint infection. Undergoing revision surgery. Current pregnancy
Intervention	Continuation of the named bDMARDs throughout the peri-operative period as prescribed prior to surgery. All other aspects of care will continue as per usual practice, including concomitant non-bDMARDs and post-surgical rehabilitation.
Control	Stoppage of bDMARDs prior to surgery and recommencing treatment after wound healing and removal of sutures/clips, according to BSR recommendations.
Planned Sample Size	394
Treatment duration	52 weeks
Follow up duration	12 months from surgery
Planned Trial Period	April 2023 to April 2025 (end of recruitment) and June 2026 (end of follow up)
Primary Outcome Measure	PROMIS-29 over the first 12 weeks post-surgery (2,4,6,9,12 weeks)

Secondary Outcome Measures	Measured at baseline, 2, 6, 12, 26 and 52 weeks post-surgery: ● Physical function: PROMIS-HAQ ● Health-related QoL: EQ-5D-5L and PROMIS-29 ● Disease activity: generic global NRS (patient) ● Medication use (glucocorticoids, antibiotics, non-biologic agents for disease control, change to or addition of a new DMARD) ● Health care resource use (NHS and non-NHS) and costs ● Disease activity: generic global NRS (physician) Measured at 2, 6, 12, 26 and 52 weeks: ● Surgical site infection • Modified 1992 Centre for Disease Control and prevention criteria for postoperative infection ● Delayed wound health: wound not closed by 2 weeks and/or dehiscence • Surgery/outcome satisfaction: Self-Administered Patient Satisfaction scale ● Adverse events including systemic infections Disease Specific outcomes will be measured at 2,6,12, 52 weeks: • Rheumatoid Arthritis: CDAI • Ankylosing Spondylitis: BASDAI, BASFI, ASAS-HI • Psoriatic Arthritis: 66/68 joint count, BSA for Skin, Leeds Enthesitis Index, Dactylitis Count, NRS

3. TRIAL FLOWCHARTS



4. BACKGROUND AND RATIONALE

4.1 Impact

Inflammatory arthritis (IA) affects around 1% of the population and includes rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS) and juvenile inflammatory arthritis (JIA). Over 400,000 people in the UK have RA, and in North America seven million people are affected, often with significant impact on quality of life.[1] A significant proportion of people with IA require long term biologic disease-modifying anti-rheumatic drugs (bDMARDs) that reduce inflammation by targeting the immune response. Although these drugs try to limit disease severity and progression, many patients continue to require planned orthopaedic surgical intervention to manage pain and restricted function caused by joint and tendon damage.[2–5] It remains unclear whether patients with IA undergoing surgery are at an increased risk of surgical site infection (SSI) and/or delayed wound healing.[4–6] The severe consequences associated with infection following orthopaedic surgery led the British Society of Rheumatology (BSR) to recommend withholding bDMARDs during the peri-operative period, despite a lack of definitive evidence.[7,8]

Withholding bDMARD treatment puts patients at an increased risk of disease flares in the post-operative period. Disease flares delay recovery, impact overall quality of life, and can severely compromise overall disease control.[9] Avoiding disease flares in the peri-operative period aids timely rehabilitation. If flares occur and disease control is lost, patients are often managed with courses of corticosteroids. Although effective in treating flares, corticosteroids increase the risk of infection in a dose-dependent fashion.[10,11] Therefore, using the lowest possible corticosteroid dosage to ensure stable IA during the peri-operative period is recommended[12] How best to balance the relative risks of peri-operative infection and disease flare remains to be established and, therefore, the question of whether to stop or continue bDMARDs in the peri-operative period has not been adequately addressed.

4.2 Current Practice

The current situation with bDMARDS is similar to that in the 1990s, when there were concerns that methotrexate (MTX) might increase the risk of postoperative complications following elective orthopaedic surgery. MTX remains the first-line ‘anchor’ DMARD in RA. Although not a bDMARD, it is immunosuppressive and is associated with an increased risk of infections. It was routine practice to discontinue methotrexate prior to elective orthopaedic surgery. Subsequently, several studies, including a prospective randomised trial and a meta-analysis, confirmed the safety of continuing methotrexate as the best option in the short-term as well as the long-term.[13–16] Consequently, it has become common practice to continue methotrexate in patients with IA undergoing planned surgery.

Based on the available published data, Goodman et al.[17] published the American College of Rheumatology (ACR) guidelines for peri-operative management of anti-rheumatic medication in patients with IA. They recommended that in cases of RA, AS, PsA and JIA, clinicians should continue the current dose of non-biologic DMARDs (such as methotrexate) for patients undergoing elective hip or knee replacement (arthroplasty). They noted that the RCTs comparing continuation vs. stoppage of DMARDs in the peri-operative period revealed that the risk of infection was decreased, not increased, when DMARDs were continued, with

RR of 0.39 (95% CI 0.17–0.91).

The recent increased availability and use of biologics in IA has brought the peri-operative management of bDMARDs into sharper focus.[18] These patients need optimal disease control to reduce the risk of flares and enable active engagement in post-operative rehabilitation, a key requisite to achieve timely recovery and optimal restoration of function. However, we lack robust data regarding the safety of continuation of bDMARDs in the peri-operative period.

4.3 Rationale for a trial

Current British Society for Rheumatology (BSR)[7] and ACR[17] guidelines reflect expert consensus based on limited and contradictory evidence. This highlights the urgent need for a large-scale multi-centre RCT to inform clinical practice. Ahead of this trial a national survey of rheumatologists (n=68) and orthopaedic surgeons (n=106) and Patient Advisory Group (PAG) meetings in two centres were undertaken. The clinician surveys confirmed considerable variation in current practice between and among both rheumatologists and orthopaedic surgeons when planning the peri-operative management of bDMARDs.[19] The PAG included 17 patients with IA on bDMARDs, who had previously undergone elective orthopaedic surgical procedures. All the stakeholders (patients, rheumatologists and surgeons) agreed that this is an important area of research and when asked, 91% said they would participate in a RCT of stoppage versus continuation of bDMARDs during orthopaedic surgery.

Two meta-analyses have looked at the risk of infection in patients on bDAMRDs compared to those who are not on bDMARDs in relation to orthopaedic surgery.[4,20] Both studies show an increased risk of surgical site infection (SSI) in patients on bDMARDs. However, these studies cannot answer the question of whether stopping the bDMARDs pre-operatively is of any benefit. Clay et al.[21] undertook a further meta-analysis specifically comparing patients who stopped bDMARDs pre-operatively to those who continued them. The authors reported a slightly higher SSI risk in those who continued bDMARDs; however, the review was based upon small numbers and had significant methodological flaws.

Overall, RA patients are at a 50%-80% greater risk of prosthetic joint infection compared to those with osteoarthritis, although the overall prevalence of these infections in both populations is low (1.26% versus 0.84% respectively).[22–25]

A comprehensive systematic review and meta-analysis was conducted and highlighted the gaps in the current evidence and the need for a RCT.[26] This lack of data together with the increasing use of these drugs, and the increase in the number of surgical procedures has highlighted the need for an RCT to aid the development of meaningful guidelines.[8]

There are no RCTs to guide practice in this area.[24,25] The most recent systematic review[26] to date on peri-operative bDMARD management (stoppage versus continuation) during orthopaedic surgery identified eleven retrospective cohort studies and no relevant RCTs. Data on postoperative infection was available for all studies, wound complications (delayed healing, dehiscence) were reported in three studies, and disease flares in four. However, data from one of the studies reporting flares could not be included in meta-analysis due to insufficient detail. The meta-analysis included 7,344 patients (4959 stoppage of bDMARDs

versus 2385 continuation of bDMARDs). The most common underlying diagnosis related to the use of bDMARDs was RA; other diagnoses included were PsA, psoriasis, JIA, AS, and inflammatory bowel disease. TNF inhibitors were the most commonly used bDMARDs, although others including abatacept, rituximab, and ustekinumab were also included. The SSI rate in patients who continued their bDMARDs was 3.06% (73/2385) compared to 2.80% (139/4959) in those who had them withheld (OR 1.11, 95% CI: 0.82-1.49). Wound healing was delayed in 2.28% (19/833) of patients who continued bDMARDs compared to 0.99% (13/1317) in those who had them withheld (OR 2.16, 95% CI: 0.48-9.85). 7.32% (3/41) of patients who continued their bDMARDs experienced disease flares compared to 25.71% (9/35) in those who had them withheld. The pooled odds ratio showed a significant decrease in disease flares when continuing bDMARDs [OR 0.22 (95% CI: 0.5-10.95) (p=0.04)]. In patients who underwent arthroplasty (joint replacement), the risk of SSI was 2.38% (46/1932) for arthroplasty patients who continued their bDMARDs and 2.32% (101/4345) in those who had them withheld (OR 1.01, 95% CI: 0.71-1.45).

5. OBJECTIVES

The overarching aim of the research is to determine the clinical effectiveness, cost effectiveness and acceptability of continuation versus stoppage of bDMARDs in patients with IA undergoing planned orthopaedic surgery.

5.1 Primary Objective

1. Assess whether continuation of bDMARDs is superior to stoppage with respect to post-operative HRQoL.

5.2 Secondary Objective

1. Undertake a 9-month internal pilot to confirm feasibility of the trial.

2. Investigate the difference between bDMARDs stoppage versus continuation for a range of secondary outcomes, including physical function, HRQoL, disease activity, medication use, health care resource use, surgical outcomes.

3. Conduct a cost-effectiveness analysis.

4. Undertake a qualitative study involving patients, rheumatologists, and surgeons.

6. TRIAL DESIGN

6.1 Summary of PERISCOPE trial design

PERISCOPE is a multi-centre, superiority RCT with an internal pilot, economic evaluation and nested qualitative study.

6.2 Primary and secondary outcome measures/endpoints

A summary of the outcome measures and time points is provided in Appendix 1.

6.2.1 Primary outcome measure

PROMIS-29 over the first 12 weeks post-surgery (2, 4, 6, 9, 12 weeks)

6.2.2 Secondary outcome measures

Clinical visits will take place at 2,6,12 and 52 weeks post-surgery, and an additional patient completed questionnaire will be collected at 26 weeks.

- Physical function: PROMIS-HAQ
- EQ-5D-5L
- Disease activity: generic global numeric rating scale (NRS) (patient)
- Surgery/outcome satisfaction: Self-Administered Patient Satisfaction scale[27]
- Health care resource use (NHS and non-NHS) and costs
- Medication use (steroids, antibiotics, non-biologic agents for disease control, change to or addition of a new DMARD)
- Disease activity: generic global NRS (physician)
- Disease specific outcome measures for each condition
- Surgical site infection: modified 1992 Centre for Disease Control and prevention criteria for postoperative infection[28]
- Delayed wound healing: A surgical wound will be considered as "healed" if by two weeks post-surgery the surgical incision has healed by primary intention without any evidence of gaping or dehiscence. Any wound that has not healed fully by primary intention by 2 weeks post-surgery, will be considered as “delayed wound healing”
- Adverse events including systemic infections

6.2.3 Disease Specific Outcome Measures

The following disease specific measures will be collected.

Rheumatoid arthritis:

- Clinical Disease Activity Index (CDAI)

Ankylosing spondylitis:

- A NRS of spinal pain
- A NRS Global Disease activity score
- The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- The Bath Ankylosing Spondylitis Functional Index (BASFI)
- Assessment of SpondyloArthritis international Society Health Index (ASAS-HI)

Psoriatic arthritis:

- 66/68 joint count measure
- Body Surface Area for skin (BSA)
- Leeds Enthesitis Index
- Total dactylitis count (0-20)
- NRS of how the disease is currently affecting them

6.3 Internal pilot and recruitment rates

An embedded pilot phase will take place over the first 9 months. The target recruitment will be 1-2 patients per month per site. The recruitment projection is based on 20 centres recruiting 1-2 patients per month (based on 4 years of audit data from Leeds and Sheffield suggesting ~80 orthopaedic surgeries/year in IA patients) with an estimated consent rate at 50% of eligible patients. Our planned recruitment assumes staggered site set-up and 50% recruitment for the first 3 months.

The pilot phase will enable assessment of the recruitment strategy using screening logs of eligibility, noting reasons for exclusion and number of patients declining participation. Where necessary, modifications will be made to the recruitment/follow-up strategy in conjunction with the input from the Patient Advisory Group (PAG), Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC), for example, revision of the consenting materials, outcome data collection and site-specific training.

6.3.1 Progression criteria

Table 1: Proposed progression criteria to be assessed at end of 9 month internal pilot

Progression criteria	Target at end of internal pilot	Green	Amber	Red
Centres open	8	100% (8)	60-99 (5-7)	<60 (<5)
Participant recruitment	1-2 patients per site per month 79 Participants recruited	100% (1-2) 100% (79)	60-99 (0.6-<1-2) 60-99 (47-78)	<60 (<0.6) <60 (<47)
Primary outcome data available	At least 80%*	100% (32)	80-99 (26-<32)	<80 (<26)

*Including participants recruited in the first 6 months

7. TRIAL SETTING

Surgery and rehabilitation will be provided in 20 NHS hospital sites representing diverse populations across the UK.

8. TRIAL ARMS

8.1 Trial intervention arm

Continuation of the named bDMARDs throughout the peri-operative period as prescribed prior to elective orthopaedic surgery. All other aspects of care will continue as per usual practice, including concomitant non-bDMARDs and post-surgical rehabilitation.

8.2 Usual care arm

Stoppage of bDMARDs prior to surgery and recommencing treatment after wound healing and removal of sutures/clips, according to BSR recommendations. Given the pragmatic nature of the PERISCOPE trial, for any instances where a participant's surgery may be delayed (for medical or non-medical reasons), it will be at clinician discretion as to whether a participant needs to recommence bDMARDs whilst surgery is rescheduled as per current clinical practice. Table 2 indicates the dosing intervals and period in which surgery should be scheduled. Treatment can be restarted when there is evidence of good wound healing (normally after two weeks), all sutures and staples are out, and there is no evidence of infection.

Table 2: Dosing Intervals of included bDMARDs

Target	bDMARDs	Dosing interval	Period in which surgery should be scheduled (relative to last dose administration)
TNF inhibitors	Adalimumab	Every 2 weeks[29]	Week 3
	Etanercept	Weekly or twice weekly[29]	Week 2
	Golimumab	Every 4 weeks[29]	Week 5
	Certolizumab pegol	Every 2 weeks[29]	Week 3
	Certolizumab pegol	Every 4 weeks[29]	Week 5
	Infliximab	Every 4, 6, or 8 weeks[29]	Week 5, 7, or 9
CTLA4-Ig	Abatacept IV	Monthly[29]	Week 5
	Abatacept S/C	Weekly[29]	Week 2
IL-6 inhibitors	Tocilizumab IV 4mg/kg	Every 4 weeks[29]	Week 5
	Tocilizumab IV 8mg/kg	Every 4 weeks[29]	Week 5
	Tocilizumab S/C	Weekly[29]	Week 3
	Sarilumab	Every 2 weeks[29]	Week 3*
IL-12/23 inhibitors	Ustekinumab	Every 12 weeks[29]	Week 13
IL-17 inhibitors	Secukinumab	Monthly	Week 5*
	Ixekizumab	Monthly	Week 5*
IL-23 p19 inhibitors	Guselkumab	Every 4 or 8 weeks	Week 5 or 9*

	Risankizumab	Every 4 weeks	Week 5*

* Period defined according to pharmacokinetic data (half-life) from drug specific SmPC.

9. PARTICIPANTS

Based on the existing evidence from systematic reviews,[26] surveys,[19] and our PAG the following decisions were made regarding eligibility:

i) Patients with RA are expected to make up the majority of the study population. However, BSR guidance concerning stoppage of bDMARDs also applies to those with AS and PsA. In addition, adult patients with JIA often require orthopaedic procedures due to the prolonged duration of their disease. It is unlikely that condition specific research would be conducted targeting these smaller groups. Therefore, we will include individuals with all these conditions in our trial.

ii) Elective orthopaedic surgery covers a broad spectrum: soft tissue surgery, soft tissue surgery with metalwork (plates/screws/wires/neurostimulators/joint fusion devices), and joint replacement. The risks of infection and delayed wound healing and their sequelae vary according to type and extent of surgery. Current guidelines do not take this into consideration. Our surveys and PAG highlighted the importance of including different surgery types within the trial. Among surgeons, 82% were willing to include soft tissue surgery cases, 70% would include those with metalwork and 64% would include patients undergoing joint replacement. Therefore, we will include all three categories of orthopaedic surgery.

iii) There is insufficient evidence to support a differential risk of serious peri-operative infection among available bDMARDs.[17] Therefore, we will include all bDMARDs used currently, except rituximab, which is typically administered per BSR guidelines 'as required' rather than at regular intervals. Consequently, drug ‘stoppage’ cannot be studied in the same way as for other bDMARDs. We will also exclude Janus Kinase (JAK) inhibitors as although they are immunosuppressant, they are not bDMARDs, they have a different mechanism of action and a very short half-life.

9.1 Inclusion criteria

- Adults aged 18 years and over
- Diagnosed with RA, PsA, or AS (including juvenile onset of all three)
- Currently prescribed one of the following bDMARDs: TNF inhibitors (adalimumab /etanercept/ golimumab/certolizumab pegol/infliximab); CTLA4-Ig (abatacept); IL-6 inhibitors (tocilizumab/sarilumab); IL-12/23 inhibitors (ustekinumab); IL-17 inhibitors (secukinumab/ixekizumab); IL-23 p19 inhibitors (guselkumab/risankizumab).
- Deemed by the clinical care team to be fit for surgery and have no contraindications to continued bDMARD use
- Scheduled to undergo elective orthopaedic surgery (Soft tissue, metalwork, or Joint replacement)
- Able to consent and complete follow-up

9.2 Exclusion criteria

- Currently prescribed JAK inhibitors
- Currently being treated with rituximab
- Current use of systemic steroids (<3 months) other than those on a stable dose of ≤5mg per day
- Previous history of native/prosthetic joint infection
- Undergoing revision surgery
- Current Pregnancy

10. TRIAL PROCEDURES

10.1 Patient identification and screening for eligibility

Potentially eligible participants will be identified by screening the waiting lists for orthopaedic surgery across the participating sites and crosschecking their details against hospital records (electronic or paper) for biologic prescription. This will be done by members of the usual care team. Some of these patients will be identified in combined rheumatology-orthopaedic multidisciplinary team clinics (MDT clinics) which take place at some of the participating sites. In addition, patients with inflammatory arthritis who are taking bDMARDs presenting to secondary care and requiring an orthopaedic surgical intervention will be screened for eligibility by the local team and approached to establish if they are potentially interested in participating in the study.

Potentially eligible participants who are interested in taking part in the study will be invited for a screening visit to formally assess eligibility and obtain informed consent. Eligibility will be formally assessed by a delegated medic.

10.2 Informed consent

Potentially eligible patients will be provided with an invitation letter and a detailed participant information sheet (PIS) which will explain the risks and benefits of trial participation clearly in text form. These may be given out in the clinic, emailed or sent by post. Sites will contact the participants by phone to check their willingness to participate in the study and to answer any questions they may have.

Following REC/HRA approval of the recruitment materials, patients who are unable to read will be provided with an audio-recording of the patient information sheet to help facilitate recruitment into the trial. A one-page pictorial decision aid will be created to help patients with literacy problems. For patients who are visually impaired we will also inform them of freely available apps on the Royal National Institute of Blind People website (https://www.rnib.org.uk/) that can help with the reading of materials. Also, if the patient is visually impaired the recruitment materials could be read out aloud by a member of staff or next of kin who would sign the witness box. For those unable to speak English, we will use either a translator or language line depending on local NHS availability. This is all part of our strategy to ensure equality, diversity and inclusivity of patients enrolled into the study at the time of consent.

Potentially eligible patients will have the opportunity to ask questions of the recruiting research team (i.e. research medic or nurse) and given as much time as they need, prior to treatment, to decide before completing consent processes, within the time constraints of clinical decisions with regards to beginning their treatment.

Consent will be recorded at the screening visit via paper consent forms, which will be uploaded onto the secure web-based data collection interface 'REDCap' once complete, or via participant e-consent directly within the REDCap system. Informed consent will be obtained by a suitably qualified and experienced local research nurse or clinician who has been authorised to do so by the Chief or Principal Investigator, as detailed on the study Delegation of Authority and Signature Log for the study site. Eligibility will be confirmed and documented in the medical notes at the screening visit, where possible. Where this is not possible, eligibility will be confirmed and documented after the screening visit and prior to the baseline visit.

The original signed form will be retained at the study site within the Investigator Site File (ISF). A copy of the signed Informed Consent will be given to participants, retained in the participant medical notes, and provided to York Trials Unit. Record of e-consent will be emailed to the participant and site for filing (where no participant email address is provided, a copy will be printed and provided to participants).

All information required by the UK Health Research Authority will be included. Throughout the entire study, screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion.

10.3 Baseline Assessment

Once participant eligibility has been confirmed and consent has been obtained (as per Section 10.2) a baseline visit will be completed to collect all baseline data (see Section 12.2)

10.4 Randomisation

Following a baseline assessment randomisation will be undertaken by local site staff using REDCap at the baseline visit. Timing of the baseline visit should ensure that at least one bDMARD dosing interval is present between the baseline visit and the date of surgery (see Table 2). The system will perform independent randomisation 1:1 (Intervention:Control), using block randomisation, stratified by underlying disease (RA/AS/PsA/JIA), type of surgery (soft tissue/metalwork/joint replacement) and sex.

10.4.1 Allocation concealment and blinding

The allocation schedule will be generated by a statistician at YTU not involved in the recruitment of participants. As this is an unblinded trial, patients and treating clinicians will be informed of the allocation. Local research teams will be asked to place the allocated patient pathway in the patient's hard copy and/or electronic case records so clinical teams have access and can refer to the document.

The participants will receive an email copy of their randomised treatment allocation, and the

participants' GPs will be informed of their treatment allocation by letter.

11. QUALITATIVE STUDY

11.1 Qualitative study overview

The intervention and management of the balance between surgical/post-operative risks versus disease control are key aspects of this research that have been confirmed by PAG members. Discussions centred on the relative risk and impact of post-operative disease flare and infection and highlighted the differences in the way the risks may be perceived by different stakeholders. Patients place great importance on risk of flares as most have experienced the impact flares have on their activities of daily living, overall well-being and participation in rehabilitation. In contrast, surgeons may place greater importance on post-operative infection risk as the consequences can be devastating. These will in turn impact on the clinician's equipoise, decision making regarding trial participation and ultimately, the implementation of study findings.

11.2 Aims

The aim of the nested qualitative study is to explore the patients' and clinicians' acceptability and experience of continuation/stoppage of bDMARDs in the perioperative period, and the impact post-operatively.

11.3 Qualitative study sampling

Qualitative interviews with patients:

Face-to-face, telephone or video interviews (via an online platform) (according to participant preference/logistics) will be undertaken with up to 30 patients (approximately 25 trial participants and 5 who declined to participate in the trial). Sampling will be according to principles of maximum variation on the basis of sociodemographic characteristics, underlying disease and randomised group.

The interviews will take place between 3 and 6 months from when the orthopaedic surgery took place. This will allow data to be collected across the recovery pathway. The interview is likely to last between 30–60 minutes. The topic guide will be informed by the PAG.

These interviews will provide vital information relating to the acceptability and experience of continuing/stopping bDMARDs in the pre-operative period and how the potential trade-off between risks of infection versus disease flare is perceived by patients. They will also provide insights into the factors that impact on patient preferences and the acceptability of risk and how information relating to the risks/benefits could best be described in the clinical setting.

Qualitative interviews with clinicians:

Semi-structured interviews will be undertaken with up to 10 orthopaedic surgeons and up to 10 rheumatologists. Sampling will ensure maximum variation on the basis of site, those involved in the delivery of the trial as well as those clinicians who declined to participate in

the proposed trial.

Ultimately, the final qualitative sample will provide for diversity and sufficient numbers to allow comparison within the analysis without oversampling. We are aiming for an adequate sample with sufficient breadth, depth and 'information power' - that is the amount of relevant information a sample holds to answer the research questions.

Data collection will focus on decision making regarding the continuation versus stopping of bDMARDs in usual care. The interviews will explore their views on the trial and willingness to change practice based on the findings, the challenges/facilitators associated with this and what information/training would be required to implement the trial findings across the NHS. The interview is likely to last approximately 30 minutes, and will take place over the telephone, or video call (via an online platform).

Site Meetings:

As part of the pilot phase, YTU staff will conduct site initiation visits (SIV) when a site indicates it is ready to go ahead with the trial. A precursor to an SIV is a preliminary meeting between YTU and a clinical team called a "pre-SIV". All pre-SIVs and SIVs will be conducted over video call and will be recorded as standard practice. These meetings hold a wealth of information about a site's attitude and ethos towards the trial and intervention. We will include the recordings of all the pre-SIV and SIV meetings as part of the qualitative analysis. This will help provide an understanding of the levers of accepting and declining site participation in the trial as well as the context in which the trial will be situated for each site.

Declining site leads:

A purposive sample of declining site leads identified during the pre-SIVs (as described above) will be recruited to take part in brief, semi-structured telephone interviews lasting around 15-20 minutes. Sampling (up to 10 participants) will be based on the information provided in the pre-SIVs relating to the reasons for decline. The interview questions will further explore the reasons for declining.

11.4 Approach and consent process

Patients: On the initial approach to potentially eligible patients, the PIS also details information on what taking part in the interviews would entail. On the main trial consent form, there is an optional consent statement for the qualitative interviews. If a participant chooses not to consent to this, it would not affect their participation in the main trial.

Where participants do consent to take part in a qualitative interview, a qualitative researcher based at the University of York will sample participants as described in the previous section, and approach them (between 3 and 6 months post-surgery) by telephone to check they are still willing to be interviewed, and arrange this.

At the beginning of the interview (prior to the audio recording starting), participants will be given a reminder of what the interview entails and given an opportunity to ask any questions

they might have. Participants will be reassured that their involvement is entirely voluntary, the interview can stop at any time and any withdrawal from the process evaluation will not affect their future medical care in any way. At the start of the audio recording participants will be asked to confirm they are happy to continue.

Clinicians taking part in the study: A member of the PERISCOPE research team (based at York Trials Unit) will approach clinicians to invite them to take part in an interview. This initial approach will be via email or a short verbal description about what participation in the research involves. Identification of clinicians for interview is likely to be based on the networks of the wider study team or via the research nurses at each site. If clinicians indicate that they are interested in being interviewed, they will be given an information sheet and opportunity to ask questions. Clinicians that agree to participate will be emailed a consent form. Prior to a phone or video interview beginning, the researcher will ask for participant's verbal consent to each item on the written consent form. Taking of this verbal consent will be audio recorded. Verbal consent and the interview will be stored as part of the same audio recording.

Declining sites leads: As with the clinicians, researchers will invite clinical leads to take part in the interview. This initial approach will be via email or a short verbal description about what participation in the research involves. Identification of interviewees will be via the recruiting YTU research team and co-Chief Investigators. If clinical leads indicate that they are interested in being interviewed, they will be given an information sheet and opportunity to ask questions. Those that agree to participate will be emailed a consent form. Prior to a phone or video interview beginning, the researcher will ask for participant's verbal consent to each item on the written consent form. Taking of this verbal consent will be audio recorded. We will also explain that we respect their informed decision to decline involvement in the trial and that the interview does not aim to challenge or change this decision, rather it aims to capture a better understanding of reasons behind declining.

Analysing recording of SIV meetings: Verbal consent for use of the recording will be collected from all members of the team who appear in the video during the meeting. If they decline, we will not include their contribution to the conversation in the analysis. There is no reference to individual patients or instances of individual care provision in these recordings.

11.3 Qualitative analysis

All interviews will be digitally audio-recorded (with consent), anonymised and transcribed, the transcripts forming the data for analysis. Qualitative data analysis will follow the principles of thematic analysis, providing an interpretive exploration of the experiences, attitudes, and beliefs of different stakeholder groups[30,31]. Emerging codes and themes will be discussed as a team and at regular intervals with the PAG. These data will be used to inform i) trial processes and recruitment optimisation and ii) what information/training would be required to implement the trial findings across the NHS on how the balance of risk can be managed optimally within the context of fully informed patient-centred care.

12. DATA COLLECTION METHODS

Data will be collected using bespoke case report forms (CRFs) completed electronically via the secure web-based outcome data collection interface 'REDCap', or collected on paper CRFs returned via free post envelopes to York Trials Unit. All reporting of data collection will be undertaken in line with the Consolidated Standards of Reporting Trials (CONSORT) statement.[32]

Participants will be followed up for the purposes of the study via self-completed questionnaires at 2,4,6,9,12, 26 weeks and 12 months. We will ask participants for full contact details at baseline (including mobile phone number, email and address) and any contact preferences. Participants will complete these at clinic visits at 2,6,12, and 52 weeks.

At 4,9,and 26 weeks a link to complete the relevant electronic questionnaire on REDCap will be sent to participants via email, with the option to send a paper copy to participants for postal completion or completion with a researcher over the phone instead as preferred. If no response is received within 1 week an automated reminder will be sent to the participant.

Investigator-completed hospital CRFs must only be completed by personnel authorised to do so by the Principal Investigator, as recorded on the trial-specific delegation log for each hospital site. Investigator-completed data can be submitted at any stage during the participant's follow-up and reminders will be sent to research staff at sites to do this.

Please see Section 11 for details of data collection for the nested qualitative study, including collection of qualitative data.

12.1 Screening Assessment

The following data will be collected by clinicians at the screening assessment:

- Confirmation of patient eligibility
- Type of Inflammatory arthritis
- Current bDMARD
- Reasons for non-consent amongst those declining participation

12.2 Baseline assessment

The following will be collected at the baseline assessment (via methods described in Section 12):

Participant completed data:

- PROMIS-29 (Patient-Reported Outcomes Measurement Information System): A validated and reliable measure that includes 7 domains: physical function, anxiety, depression, fatigue, sleep disturbance, ability to participate in social roles and activities and pain interference.
- PROMIS Health Assessment Questionnaire (PROMIS-HAQ): An assessment of physical functioning. The PROMIS-HAQ assesses function categorised into eight

subsections, including dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities over a one-week time period.
- EQ-5D-5L: a validated, generic health status measure asking 5 questions on mobility, self-care, usual activities, pain and discomfort, and anxiety and depression, accompanied by a health status thermometer visual analogue scale (VAS).
- Disease activity using a general global NRS (patient completed)
- Health care resource use (NHS and non-NHS) and costs
- Disease specific measures

Investigator completed data

- Demographic information (e.g., age/DOB, gender, employment status, ethnicity, height, weight)
- Disease history (e.g. year of diagnosis)
- Current and previous DMARD use
- Disease activity using a general global NRS (physician completed)
- Disease specific measures

12.3 Follow up assessments

12.3.1 Participant completed data

The following will be collected from patients within questionnaires at 2,6,12, 26 weeks and 12 months post-surgery (see Appendix 1). The PROMIS-29 will also be collected from participants at 4 and 9 weeks postoperatively. If surgery is cancelled and will not be rescheduled, follow-up will begin from the date of cancellation.

- PROMIS-29
- PROMIS-HAQ
- EQ-5D-5L
- Disease activity using a general global NRS (patient completed)
- Surgery/outcome satisfaction: Self-Administered Patient Satisfaction scale
- Health care resource use (NHS and non-NHS) and costs

A link to complete these electronically on REDCap will be sent to patients via email with alternative options available for completion via phone/post available as required/appropriate (see 12 for further information).

12.3.2 Investigator (local site research team) completed data

The following will be collected by the local site research team during the 12-month post-surgery follow up period for each participant and will be recorded on the electronic CRF via REDCap. Investigator-completed data can be submitted at any stage during the participant's follow-up and reminders will be sent to research staff at sites to do this monthly.

- Medication use (steroids, antibiotics, non-biologic DMARDs, change to or addition of a new DMARD)

- Disease activity using a generic global NRS
- Disease specific outcome measures for each condition
- A modified 1992 Centre for Disease Control and prevention criteria for postoperative infection: This is a measure to assess surgical site infection.
- Delayed wound health: A surgical wound will be considered as "healed" if by two weeks post-surgery the surgical incision has healed by primary intention without any evidence of gaping or dehiscence.
- Adverse events including systemic and/or surgical site infections

12.3.3 Disease Specific Measures

The disease specific measures will be collected at the visits at 2,6,12, and 52 weeks. Many of these measures combine clinician and patient ratings and so will be collected at the clinic visits only. The following measures will be collected and where clinician ratings are required will be completed by appropriately trained health care professionals.

Rheumatoid arthritis:

• CDAI: This measure has 4 components: tender and swollen joint counts, and patient's and physician's global assessments of disease activity on a NRS

Ankylosing spondylitis:

• A NRS of spinal pain: The question referring to total pain in the spine due to AS (ie, “How much pain of your spine due to spondylitis do you have?”) will be used.[33] When responding to each question, the subject is to consider the average amount of pain in the preceding week on a scale from 0 - 10.
• BASDAI: The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)[34] [is a validated self-reported instrument to measure disease activity which consists of six 10-unit horizontal NRS to measure severity of fatigue, spinal and peripheral joint pain and swelling, enthesitis, and morning stiffness (both severity and duration, respectively) over the last week. The final BASDAI score ranges from 0 to 10.
• NRS Global Disease activity score: The Patient Global Assessment of Disease Activity (PGDA) is scored in response to the question “How active was your spondylitis on average during the last week?” using a NRS where 0 is “not active” and 10 is “very active”
• BASFI: The Bath Ankylosing Spondylitis Functional Index (BASFI) is a validated disease-specific instrument for assessing physical function[35] comprising 10 items relating to the past week. The NRS version will be used for the answering options of each item on a scale of 0 (“Easy”) to 10 (“Impossible”). The BASFI is the mean of the 10 scores such that the total score ranges from 0 to 10, with lower scores indicating better physical function.
• ASAS-HI: The ASAS Health Index (ASAS-HI) is a self-report questionnaire which measures functioning and health across 17 aspects of health and 9 environmental factors (EF)[36] The ASAS HI contains items addressing categories of pain, emotional functions, sleep, sexual function, mobility, self-care, and community life. The EF Item Set contains items addressing categories of support/relationships, attitudes and health services. Validation was done in patients with radiographic and non-radiographic axial SpA and peripheral SpA.

Psoriatic arthritis:

• 66/68 joint count measure: This measure is an assessment of 66 joints for swelling and 68 joints for tenderness.
• BSA for skin: This is a clinician assessment of body surface area affected by psoriasis
• Leeds Enthesitis Index: This assesses whether tenderness or pain is present at 6 sites.
• Total dactylitis count (0-20): This is an assessment of the 20 fingers and toes to assess how many are swollen from the base to the tip.
• NRS: In all the ways in which your PSORIASIS and ARTHRITIS affects you, how would you rate the way you felt over the past week.

12.4 Managing change of participant status

Patients will be able to change status and/or withdraw completely from the study at any time without implication. If a patient requests this, the local research team will clarify what aspect of the trial the patient is withdrawing from: for example, withdrawal from ongoing data participation/data collection; withdrawal from the trial in full. Patients who request to change status will be invited to complete a withdrawal form, which will otherwise be completed by the local trial team and sent to the YTU. All participants will be provided with contact details of local and central research teams' for queries, etc.

It is unusual for this cohort of patients to lose capacity during treatment. If participants did lose capacity after trial enrolment, Identifiable data already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. We would withdraw the participant from completion of patient questionnaires.

12.5 End of Trial

The end of the trial will be defined as last patient, last visit (LPLV), the date that the last patient reaches the last follow up time point, i.e. 12 months after date of surgery.

13. SAFETY REPORTING

13.1 Risks and anticipated benefits

Patients with inflammatory arthritis undergoing elective orthopaedic surgery are perceived to be at higher risk of infection and/or flares post-surgery. This is irrespective of whether they are part of the study or not. At present, the routine practice is to stop the biologic DMARDs pre-operatively to reduce the risk of infection although this does increase the potential for disease flares, which in turn delays recovery, may need steroid administration which in turn can increase risk of infection. In addition, it is not known whether the risk of infection will increase if the biologics are continued peri-operatively. Therefore, in addition to the usual risks of any surgery, the patients participating in this study are potentially at an increased risk of infection (particularly for those who continue biologics) and flares (particularly for those who stop biologics). However, there is a lack of evidence regarding the safety of

continuation of bDMARDs in the perioperative period. The PERISCOPE trial aims to fill this evidence gap.

Meetings with the PERISCOPE PAG, a stakeholder survey, and discussions with key stakeholders, suggests a pragmatic RCT comparing continuation vs stoppage of bDMARDS for patients with IA undergoing elective orthopaedic surgery during the peri-operative period is feasible, ethical, and required. If the trial shows positive results, patients may benefit by receiving optimal disease control to reduce the risk of flares and enable active engagement in post-operative rehabilitation, a key requisite to achieve timely recovery and optimal restoration of function.

We will adhere to the Research Governance Framework/ UK Policy Framework for Health and Social Care Research and Good Clinical Practice. The participant information sheet for the study will be developed with the involvement of service users and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants after they have had sufficient time to read the study materials and ask questions.

13.2.1 Adverse Events (AEs)

The PERISCOPE trial will comprise adult patients undergoing orthopaedic surgery. Prolonged hospital inpatient admission is normal in this group of patients. For the purposes of the PERISCOPE trial, (AE) are defined as any untoward medical occurrence (i.e. any unfavourable and unintended sign, symptom or disease), experienced by a clinical trial participant and which is temporally associated with study treatment (interventions or control) and/or is related to the study intervention or control treatments. Possible adverse events could include surgical site infection, systemic infection, and venous thromboembolism.

Sites should report adverse events when there is concern and consider this in relation to section 13.2.2 below, and the study team will help to determine relevance

13.2.2 Serious Adverse Events (SAEs)

A serious adverse event is any untoward medical occurrence that:

- results in death
- is life-threatening*
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

*NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the YTU

13.3 Reporting procedures for (S)AEs

All AEs occurring during the study observed by the investigator or reported by the participant, will be recorded on the PERISCOPE Adverse Event Form for return to York Trials Unit.

The following information will be recorded: description, date of onset and end date, assessment of relatedness to study intervention and/or procedures, outcome, expectedness and action taken. Follow-up information should be provided as necessary.

Where repeated adverse events of similar type are observed, these will be discussed with the Data Monitoring and Ethics Committee (DMEC) and will be onward reported should concerns be raised in relation to the type of event and/or frequency observed.

All SAEs will be entered onto the SAE reporting form and sent via REDCap or encrypted email to YTU within 24 hours of the investigator becoming aware of the event. Once received, causality and expectedness will be confirmed by the Chief Investigator (CI) or a medical co-applicant or Trial Steering Committee (TSC) member not acting as a site Principal Investigator (PI). Any change of condition or other follow-up information should be sent as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

SAEs that are deemed to be unexpected and related to the trial will be notified to the REC and sponsor within 15 days by York Trials Unit. All such events will be reported to the TSC and DMEC at their next meetings.

Any pregnancy occurring during the trial, and the outcome of the pregnancy, will be recorded. These patients will be managed as per standard of care. The local research nurse or clinician will question patients about their pregnancy status as per routine practice.

13.4 Reporting urgent safety measures

An “urgent safety measure” is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the REC, in order to protect clinical trial participants from any immediate hazard to their health and safety.

If any urgent safety measures are taken by an investigator, these must be reported to YTU within 24 hours. YTU will take responsibility for reporting of urgent safety measures to the Sponsor within 1 working day (if not already aware) and the relevant REC if required.

14. STATISTICS AND DATA ANALYSIS

14.1 Statistical analysis plan

Analyses will be described in detail in a Statistical Analysis Plan (SAP), which will be finalised prior to the end of data collection and reviewed and approved by the independent data monitoring committee. Analyses will be carried out on a locked dataset and performed using two-sided statistical tests at 5% significance under the principles of intention-to-treat. All analyses will be conducted taking into consideration the reporting requirements of the Consolidated Standards of Reporting Trials (CONSORT).[32]

14.2 Sample size calculation

The MCID for the HAQ-DI is well established and found to lie between 0.25 and 0.35 in IA (48), with a standard deviation of 0.68 (68). The MCID for PROMIS-29 is less well established; therefore, to look for the same magnitude of effect as that for the HAQ-DI, assuming 90% power, 5% alpha, effect size 0.37 and 20% attrition, 394 participants would need to be randomised. When using patient anchors in a population with rheumatoid arthritis, 1 to 3 points was generally the change in scores when patients reported they were a little better or a little worse and meaningful change was associated with at least 3 to 5 points change.[37] Within this population, the effect size of 0.37 would translate to a MCID of 3.7, which is in line with early evidence from within a relevant context.

14.3 Statistical analysis methods

The primary analysis will be by intention-to-treat and will follow CONSORT reporting guidelines for a superiority study. A detailed statistical analysis plan (SAP) will be written before the follow-up period concludes. In the primary analysis, we will compare the primary outcome between groups using a covariance pattern mixed-effect linear regression model, incorporating post-randomisation time points. Treatment groups, time point, treatment-by time interaction and baseline covariates will be included as fixed effects. Participants will be included as a random effect accounting for repeated observations per patient. Estimates and 95% CIs will be extracted from the model with the estimate over 12 weeks as the primary outcome of interest. In the primary analysis model, any missing outcome data will be assumed to be missing at random. Patterns of missingness will be explored, and a sensitivity analysis will be considered to assess departures from the missing at random assumption using a pattern mixture model.

Two exploratory subgroup analyses to investigate the potential differential effect of the intervention by the type of surgery and underlying disease will be undertaken. These will be implemented by the addition of an interaction term between the relevant factor and randomised group in the primary analysis model. Continuous secondary outcome measures will be analysed using the same type of model as that for the primary outcome. Delayed wound healing and surgical site infections will be compared using a generalised linear model; risk differences and relative risk will be reported. Harms will be reported descriptively, including the number and nature of (serious) adverse events and number of participants with at least one (serious) adverse event. Medication use will also be reported descriptively.

14.4 Cost-effectiveness analysis

The cost-effectiveness of bDMARD continuation compared with bDMARD stoppage will be evaluated using a within-trial cost-utility analysis, from the perspective of the NHS and personal social services, over 12 months. Participant level data regarding health-related quality of life, resource use and costs will be collected over a 12-month period, using self-completed questionnaires (at baseline, 2, 6, 12, 26 and 52 weeks post-randomisation) and hospital case report forms, and compared for the bDMARD continuation and stoppage groups. Participants' utilisation of healthcare services will be collected via resource use questions, for secondary care (i.e. hospital inpatient stays, accident and emergency attendances, day cases, and outpatient attendances) and primary care (i.e. GP, nurse, physiotherapy). The cost of disease flares, surgical site infections, delayed wound healing and other complications encountered by participants over the trial's 12-month follow-up period will thereby be captured. Costs regarding medication use will also be incorporated (i.e. antibiotics, bDMARDs, and other medications for disease control). Unit costs will be obtained from established costing sources[38–40] and attached to each resource item/medication to generate total cost estimates for each participant. Further costs will be collected for a secondary analysis, to explore the impact of private expenditures (i.e. out-of-pocket medication expenditure, travel costs for appointments) and lost productivity on cost-effectiveness findings.

Health outcomes will be measured in terms of QALYs, based on participants' health-related quality of life, using the EQ-5D-5L[41] in the base case. In addition, a sensitivity analysis will use participants' PROMIS-29 responses to generate utilities, using the PROMIS Preference (PROPr) scoring system.[42] The total QALYs accrued by each participant during the 12 months will be estimated using the area under the curve method.[41] Mean within-trial estimates of health benefits and costs will be generated by means of regression methods, allowing for correlation between costs and utilities, and adjusting for key covariates (including baseline utility). Non-parametric bootstrapping will be used to account for skewed and missing data. Missing data patterns will be analysed and used to guide the multiple imputation methods employed to deal with missing data.[43] The findings will be presented as mean costs and effects for both groups, as incremental cost-effectiveness ratios (i.e. incremental cost per QALY gained) and net health benefit at 12 months. Confidence intervals and cost-effectiveness acceptability curves[44] will be used to describe uncertainty around the analysis findings. Sensitivity analyses will explore the impact of varying key cost parameters and assumptions underpinning the analysis model in terms of the cost effectiveness findings. Analyses will take an intention-to-treat approach. If deemed appropriate (i.e. dependent on the trial's results and data availability), the economic findings will be extrapolated beyond the trial's 12 month time horizon. Data from the trial will be combined with published data to estimate the long-term impact, thereby estimating long-term costs for patients who develop a deep infection, for instance. All analyses will follow NICE guidance,[31] with full details provided in a Health Economics Analysis Plan.

15. DATA MANAGEMENT

15.1 Data entry and reconciliation

The data collected by sites will be entered onto the secure web-based REDCap interface. Data will be held securely on a cloud-hosted REDCap server. Access to the study interface will be restricted to named authorised individuals granted user rights by a REDCap administrator at YTU.

The staff involved in the trial (both at the sites and YTU) will receive training on data protection. The staff will be monitored to ensure compliance with privacy standards. A detailed Data Protection Impact Assessment (DPIA) for the trial will be developed for approval by the relevant parties.

Data will be checked according to procedures detailed in the trial specific Data Management Plan.

15.2 Data storage and archiving

Each site will hold data according to the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. Data will be collated electronically via the secure online data collection software “REDCap” or paper CRFs and questionnaires in some cases (e.g. where a participant requests completion of a questionnaire in paper form). CRFs will be identified by a unique identification number (i.e. the Trial number) only. A Trial Enrolment Log at the sites will list the ID numbers. YTU will maintain a list of trial numbers for all trial patients at each site.

All YTU data recorded electronically will be held in a secure environment with permissions for access as detailed in the delegation log. The Department of Health Sciences, in which YTU is based at the University of York, has a backup procedure approved by auditors for disaster recovery. Full data backups are performed nightly using rotational tapes, to provide five years’ of recoverable data. The tape backup sessions are encrypted and password protected, with tapes stored in a locked fire-proof safe in a separate secured and alarmed location. All study files will be stored in accordance with Good Clinical Practice guidelines. Study documents (paper and electronic) held at YTU will be retained in a secure (kept locked when not in use) location for the duration of the trial. Once sites have completed a close out report and this is approved by the Sponsor, they will be instructed to archive their site file and trial data according to their local SOPs.

All essential study documents, including source documents, will be retained for a minimum period of ten years after study completion, in line with the Sponsors’ policy. The separate archival of electronic data will be performed at the end of the trial, to safeguard the data for the period(s) established by relevant regulatory requirements. No archived documents/data will be destroyed without authorisation from the Sponsor.

The electronic data will be stored for a minimum of 10 years in electronic format in accordance with guidelines on Good Research Practice. All electronic records will be stored on a password protected server. All paper records will be stored in a secure storage facility or off-site by York Trials Unit.

Essential documents will initially be stored in the YTU archive room. Once regular access is no longer required, they will be relocated to the YTU approved off-site archive provider, DeepStore Ltd. Permission from the lead statistician will be needed to request access.

Electronic records will be stored on an electronic archive drive only accessible by named people.

All work will be conducted following the University of York's data protection policy which is publically available (Data Protection - Records Management and Information Governance, University of York).

15.3 Participant confidentiality and data protection

The researchers and clinical care teams must assure that patients' anonymity will be maintained and that their identities are protected from unauthorised parties. Patients will be assigned a Unique Trial Number, and this will be used on CRFs; patients will not be identified by their name in order to maintain confidentiality.

Data will be processed in accordance with the General Data Protection Regulations (GDPR) and the Data Protection Act 2018. All records will be kept in secure locked locations. All consent forms will be securely stored on password protected, authorised access only, servers and/or in a secure locked cabinet. Clinical information will only be accessed by responsible individuals from the study team, the Sponsor, the NHS Trust, or from regulatory authorities; where it is relevant to the patient taking part in this research as he/she would have agreed to at the time of consent.

The University of Leeds and University of York will be joint data controllers. Documents/data will be stored for a minimum of 10 years after trial completion.

15.4 Reporting Protocol Deviations and Breaches

Any deviations from the protocol will be reported to York Trials Unit using a protocol deviation log. Details of corrective and preventative actions will be recorded to mitigate the deviation and prevent recurrence.

Any deviation from the protocol which is like to effect to a significant degree either:

i) the safety or physical or mental integrity of the participants of the trial; or
ii) the scientific value of the trial

will be considered a serious breach and will be reported to YTU within 24 hours of being made aware of the breach. YTU will take responsibility for reporting of serious breaches to the Sponsor within 1 working day (if not already aware) and the relevant REC if required.

16. QUALITY CONTROL AND ASSURANCE

16.1 Trial Management Group

A Trial Management Group (TMG) has been established to oversee the day-to-day management (e.g. protocol and ethics approvals, set-up, recruitment, data collection, data management) of the study, and is chaired by York Trials Unit. Membership will include the co-CIs, co-investigators, research staff on the project and PAG representation (two slots).

The role of the TMG is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. Throughout the project there will be regular teleconference contact supplemented by face-to-face meetings where required. Frequency of meetings will vary depending on the stage of the trial but at least monthly during the early stages and pilot.

16.2 Data Monitoring and Ethics Committee

The study will be regularly reviewed by the independent Data Monitoring and Ethics Committee (DMEC) composed of independent clinicians and health service researchers with appropriate expertise.

The DMEC will meet routinely to provide project oversight to the trial. This will include monitoring safety and efficacy data as well as quality and compliance data and ensuring that the protocol is accurately followed, and the study is GCP compliant. The committee will recommend whether there are any ethical or safety reasons why the trial should not continue. The independent members of the DMEC committee will be allowed to see unblinded data.

The DMEC will meet at least annually or more frequently if the committee requests. The minutes/records of these meetings will be stored at YTU and will be shared with the sponsor on a routine basis.

16.3 Trial Steering Committee (TSC)

An independent TSC has been established to provide overall independent oversight for PERISCOPE on behalf of the Sponsor and Project Funder and to ensure that the project is conducted to the rigorous standards set out in the Department of Health's Research Governance Framework for Health and Social Care and the Guidelines for Good Clinical Practice. The TSC will meet routinely during the trial and will monitor the progress of the trial and provide independent advice. Amongst its members will be an independent chair (methodologist), two public/patient contributors, a consultant orthopaedic surgeon and consultant rheumatologist who are independent of the study research team, and who have expertise in the research area. A Sponsor representative will also be invited to attend the TSC meeting.

17. MONITORING, AUDIT & INSPECTION

YTU will develop a Trial Monitoring Plan which will be agreed by the Sponsor, Trial Management Group (TMG), TSC and CI's based on the trial risk assessment. No routine on-site monitoring will take place, however regular central monitoring will be performed according to GCP and the PERISCOPE Monitoring Plan. Data will be evaluated for compliance with the protocol and GCP and the applicable regulatory requirements.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Ethics and approvals

We will adhere to the UK Framework for Health and Social Care Research[45].[46]. The PIS for the study will be developed with the involvement of service users and our PPI/PAG groups and will give a balanced account of the possible benefits and known risks of the interventions. It will state explicitly that quality of care will not be compromised if the participant decides to a) not enter the trial or b) withdraw their consent. We will make it clear that there is no obligation to participate. Written informed consent will be obtained from all participants after they have had sufficient time to read the study materials and ask questions. An application for ethical approval will be made in set-up, which will include all participant documentation. We do not anticipate major ethical concerns with this study.

We will seek national Health Research Authority (HRA) & Research Ethics Committee (REC) approval via the Integrated Research Ethics Application System (IRAS) system for the study. The local R&D departments of participating hospitals will approve their involvement in the trial. The trial will be subject to DMEC oversight. The trial manager/CI will submit and obtain approval from the above for all substantial amendments to the original approved documents.

18.2 Amendments

Once the TMG have agreed that an amendment is necessary, the amendments will be made to the required documentation and the HRA amendment tool completed. This tool will confirm the category of the amendment. Once Sponsor authorisation has been confirmed, YTU will submit and, where necessary, obtain approval from the Research Ethics Committee (REC), Health Regulatory Authority (HRA) and host institution(s) for approval of all substantial amendments to the original approved documents. Once approvals are received, the new documents/versions will be shared with sites and the study version control log will be updated for sites to check they are using only the most recent versions of trial documents.

18.3 GCP/Declaration of Helsinki

The Investigators will ensure that this study is conducted in full conformity with current regulations, the current revision of the Declaration of Helsinki, and with the principles of Good Clinical Practice.

19. PATIENT AND PUBLIC INVOLVEMENT (PPI)

In preparation for the PERISCOPE trial a number of patient advisory group (PAG) meetings have been conducted. The patient engagement work has included 17 people with IA (RA, PsA, AS and JIA: all represented) who are taking bDMARDs and have had orthopaedic surgery. The study protocol presented here was co-produced with the PAG, including inclusion and exclusion criteria, study schedule and primary and secondary outcome measures, including outcome assessment tools, as well as ways to support diversity and inclusivity in PERISCOPE.

The PAG will continue to work with the study team to enhance recruitment by co-developing study documents and communication tools (written and pictorial). They will ensure dissemination of findings is accessible and engaging for patients, their carers, and the public, including historically underserved communities. Importantly, the PAG will co-produce

the content for our patient facing website and support our patient open days when research findings will be disseminated to the wider general public. Our highly experienced PPI manager will support the PPI co-applicants to ensure they are appropriately engaged and not overburdened.

The PAG will meet regularly throughout the study, with Leeds and Oxford members working together to ensure wider representation. Two PPI member places will be reserved on each of the trial steering committee (TSC) and trial management group (TMG), with only one PPI member required to attend each meeting. This will reduce the burden on individuals in the PAG. Two PAG members have agreed to be part of the TSC and two others have agreed to be part of the TMG. Two of these four members have a track-record of providing extensive support within the Leeds PPI group and are regular participants in our (Leeds) Biomedical Research Centre (BRC) PPI meetings. They will provide mentorship for those new to PPI activities.

The PAG will continue to meet 6 monthly throughout the trial. The trial manager will join the group. The PAG will feed back to the TSC via the nominated committee members. We will engage with the NIHR Centre for Engagement and Dissemination to optimise training and support for PPI input and activities. Our PPI manager will provide in-house training for all PAG members. Oversight of PPI activities will be provided by Dr Mankia (co-CI, Leeds) and Dr Coates (Oxford). We will follow NIHR guidelines for the recognition and payment of all PPI services.

20. FINANCING AND INSURANCE

20.1 Finance

The PERISCOPE Trial is funded by the Health Technology Assessment Programme (NIHR 134800). The financial arrangements for the study will be as contractually agreed between the funder, the University of York and the Sponsor (University of Leeds).

20.2 Indemnity

‘The University of Leeds, when acting as Sponsor, has insurance cover in force, which meets claims against it and where those claims arise from the Universities own negligence in its role and activities relating to the study (and which is subject to the terms, conditions and exceptions of the relevant policy). Clinical negligence indemnification will rest with the participating NHS Trust under standard NHS arrangements.

21. DISSEMINATION AND PROJECTED OUTPUTS

A publications policy will be generated in advance to detail authorship, acknowledgements and review processes for any publications arising from the PERISCOPE Trial.

Given the current lack of high-quality evidence on this topic, the findings from PERISCOPE would feed directly into practice guidelines for the use of biologics at the time of orthopaedic surgery. Dissemination will focus on supporting the wider adoption and implementation of

the research findings. The trial results, alongside findings from the qualitative work, will inform the optimal approach to how the evidence should be described to key stakeholders in order to facilitate patient and clinician decision making as part of high-quality patient-centred care.

The study protocol will be published in a peer reviewed journal after the study commences. A HTA monograph of the findings will be produced as well as publications in other high impact peer reviewed journals.

A range of methods will be used to target groups for whom the results (and implementation plan) will be relevant. In addition to academic journals, we will use lay summaries targeted at specific stakeholders, presentations at relevant professional society events and press releases through the collaborating NHS organisations, occupational health service organisations and universities. Regular attendance of clinical co-applicants at professional events and conferences will allow cost-effective dissemination of the findings.

Key stakeholders will be targeted through a range of organisations/bodies such as: Royal College of Surgeons, British Orthopaedic Association and affiliation specialist societies (British Hip / Knee / Foot and Ankle/ Shoulder and Elbow/ Hand Societies), British Society for Rheumatology (BSR), British Society for Spondyloarthritis (BRITSpA) European Alliance of Associations for Rheumatology (EULAR), National Rheumatoid Arthritis Society, American College of Rheumatology (ACR), American Association of Orthopaedic Surgeons (AAOS) and Versus Arthritis (VA).

The PAG will oversee the detailed dissemination strategy for this study and will provide input into the materials presented; for example, an annual newsletter, co-written with PAG members will be sent to all trial participants. A plain English summary will be disseminated to trial participants who have expressed an interest in hearing about the findings. The results will also be disseminated more widely to patients by ensuring that the key websites, that patients undergoing surgery use, are updated with relevant information for example the Royal College of Surgeons of England information webpage https://www.rcseng.ac.uk/patient-care/recovering-from-surgery/total-hip-replacement/returning-to-work/. In addition, PAG members will use their community links to inform the wider population of study findings.

Dissemination will follow best practice outlined by the NIHR, including patient facing webinars, scientific presentations, open access publications, professional bulletins, social media and developing national guidelines. All publications, presentations, correspondence and advertisements arising or related to the grant will acknowledge the funder using the National Institute of Health Research (NIHR) approved disclaimer.

21.1 Authorship eligibility guidelines

Authors for any publications deriving from this protocol will be required to meet The International Committee of Medical Journal Editors (IJCMJE) has defined authorship criteria for manuscripts submitted for publication. All key protocol contributors will be provided the opportunity to fulfil IJCMJE author criteria.

Details of planned publications and requirements for authorship will be detailed in a publication plan.

22. ACCESS TO DATA

A statement of permission to access source data by study staff and for regulatory and audit purposes will be included within the patient consent form with explicit explanation as part of the consent process and Participant Information Leaflet.

In principle, once YTU has completed the analysis and completed all intended outputs, anonymised data will be made available for meta-analysis and where requested by other authorised researchers and journals for publication purposes. Requests for access to data will be reviewed by the Chief Investigator and study Sponsor.

The Investigator(s)/Institutions will permit monitoring, audits, and REC review (as applicable) and provide direct access to source data and documents.

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24. APPENDICES

Appendix 1: Schedule of outcomes and timepoints

	TIMEPOINTS								
	Screening	Baseline	2 weeks	4 weeks	6 weeks	9 weeks	12 weeks	26 weeks	52 weeks
Participant assessments									
Demographic information		X							
PROMIS-29		X	X	X	X	X	X	X	X
PROMIS-HAQ		X	X		X		X	X	X
EQ-5D-5L		X	X		X		X	X	X
Surgery/outcome Patient satisfaction scale			X		X		X	X	X
Disease activity using a general global NRS (patient)		X	X		X		X	X	X
Health Resource use		X	X		X		X	X	X
Disease Specific Outcome Measures *		X	X		X		X		X
Investigator assessments									
Eligibility Confirmation	X								
Medication use		X	X		X		X		X
Disease activity using a generic global NRS (physician)		X	X		X		X		X
Disease specific outcome measures *		X	X		X		X		X
A modified 1992 Centre for Disease Control and prevention criteria for postoperative infection			X		X		X		X
Assessment for delayed wound healing			X		X		X		X
Adverse events			X		X		X		X

* Disease specific outcomes: **RA**: CDAI; **AS**: BASFI, BASDAI, ASDAS, ASAS-HI, NRS; **PsA:** 66/68 joint count, BSA for Skin, LEI, NRS