IRAS ID: 1010810

iFIT

UK-MRA Myeloma XVIII

Immunotherapy approaches adapted for **fit**ness in newly diagnosed transplant ineligible patients with Myeloma

Version 2.0, 17 September 2025

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Developed in association with the UK Myeloma Research Alliance (UK-MRA)

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Sponsor Reference Number:	2024-CT02
NIHR CPMS ID:	70417

This protocol has regard for the HRA guidance.

This protocol is divided into several parts:

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4. TRIAL SUMMARY

Trial Title	**iFIT** iFIT (UK-MRA Myeloma XVIII): **I**mmunotherapy approaches adapted for **fit**ness in newly diagnosed transplant ineligible patients with Myeloma	
Clinical Phase	Phase III	
Trial Design	Biomarker-stratified, platform trial	
Trial Participants	Transplant ineligible newly diagnosed multiple myeloma	
Planned Sample Size	1,226	
Planned Trial Period	Planned recruitment (48 months): August 2025 – July 2029 Planned active follow-up (36 months): August 2029 – July 2032 Planned long-term follow-up (48 months): August 2032 – July 2036	
	Objectives	Outcome Measures
Primary	**iFIT1**: Progression-free survival (PFS)	The time from iFIT1 randomisation to progression or death from any cause.
	iFIT2: Event-free survival (EFS)	The time from iFIT2 randomisation to the first of the following events: grade 4 haematological AEs (anaemia, neutropenia, thrombocytopenia), grade 3 and 4 non-haematological AEs (including Second Primary Malignancies (SPMs)), discontinuation of trial treatment, progression or death.
	iFIT3: Progression-free survival (PFS) and quality of life (QoL)	<u>Progression-free survival</u> The time from **iFIT3** randomisation to progression or death from any cause. <u>Participant-reported overall health and QoL</u> The global health status (GHS)/QoL scale score of the European Organisation for Research and Treatment of Cancer (EORTC) EORTC QLQ-C30 [1] at 30 months after **iFIT3** randomisation.

<table>
<tr><td>Investigational Medicinal Products (IMPs)</td><td>Daratumumab, lenalidomide, dexamethasone, teclistamab, talquetamab</td></tr>
<tr><td>Treatment duration, Formulation, Dose, Route of Administration</td><td>

<u>Standard of care induction (n=1,226):</u>

6 cycles of DRd treatment

	STANDARD DOSE*	**Days**
D	1,800mg	Cycle 1 and 2: 1, 8, 15 and 22 Cycle 3-6: 1 and 15
R	25mg	1 – 21
d	40mg in participants ≤ 75 years 20mg in participants ≥ 76 years	1, 8, 15 and 22

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply
Dexamethasone: oral tablets, solution or subcutaneous injection, NHS supply

<u>iFIT1 (MRD+; FIT/UNFIT) (n=652, 1:1:1)</u>

One of:

<u>Continue DRd to PD</u>

	STANDARD DOSE*	**Days**
D	1,800mg	1
R	25mg	1 – 21
d	40mg in participants ≤ 75 years 20mg in participants ≥ 76 years	1, 8, 15 and 22

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply
Dexamethasone: oral tablets, solution or subcutaneous injection, NHS supply

<u>Dara-Tec for 18 cycles and then active monitoring until PD</u>

Drug	**iFIT1 cycle**	**Dose**	**Day(s)**
Dara	1-18	1,800mg	1
TEC	1 (step-up dosing)	0.06mg/kg	1
		0.3mg/kg	3
		1.5mg/kg	8
	1	1.5mg/kg	15
	2-18	3mg/kg	1

Daratumumab: subcutaneous injection, trial supply
Teclistamab: subcutaneous injection, trial supply
Patients should be admitted for monitoring or remain close to the hospital for 48 hours after the shaded doses.

<u>Dara-Tal for 18 cycles and then active monitoring until PD</u>

Drug	**iFIT1 cycle**	**Dose**	**Day(s)**
Dara	1-18	1,800mg	1
TAL	1 (step-up dosing)	0.01mg/kg	1
		0.06mg/kg	3
		0.4mg/kg	8
		0.8mg/kg	15
	2-6	0.8mg/kg	1 and 15
	7-18	0.8mg/kg	1

Daratumumab: subcutaneous injection, trial supply
Talquetamab: subcutaneous injection, trial supply
Patients should be admitted for monitoring or remain close to the hospital for 48 hours after the shaded doses.

</td></tr>
</table>

iFIT2 (MRD+; FRAIL) (n=279, 1:1)

One of:

Continue DRd to PD

	STANDARD DOSE*	Days
D	1,800mg	1
R	25mg	1 – 21
d	40mg in participants ≤ 75 years 20mg in participants ≥ 76 years	1, 8, 15 and 22

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply
Dexamethasone: oral tablets, solution or subcutaneous injection, NHS supply

Continue DR to PD

	STANDARD DOSE*	Days
D	1,800mg	1
R	25mg	1 – 21

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply

iFIT3 (MRD-) (n=233, 1:1)

One of:

Continue DR to PD

	STANDARD DOSE*	Days
D	1,800mg	1
R	25mg	1 – 21

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply

Continue DR for 18 cycles and then active monitoring until PD

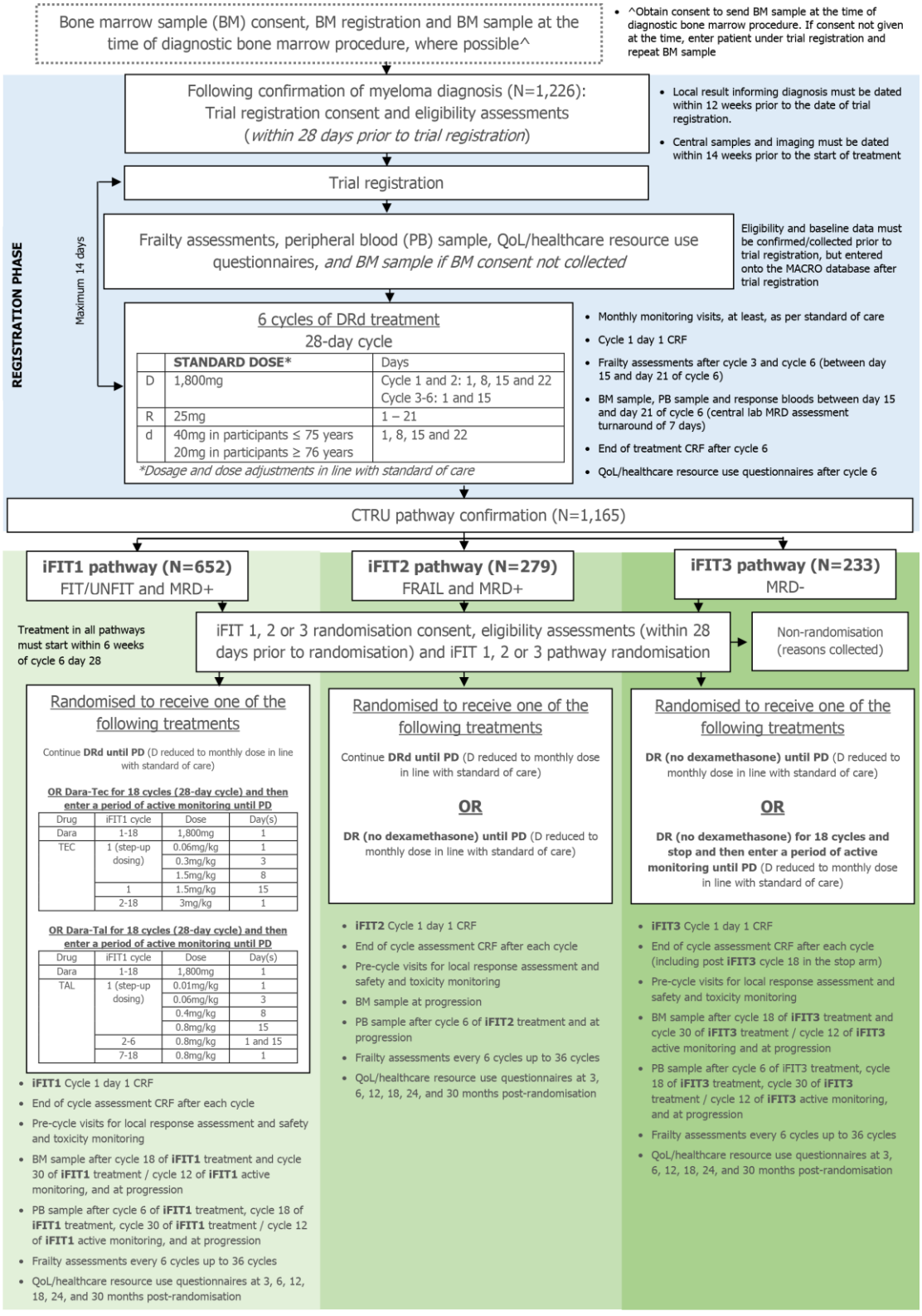
	iFIT3 cycle	STANDARD DOSE*	Days
D	1-18	1,800mg	1
R	1-18	25mg	1 – 21

Daratumumab: subcutaneous injection, NHS supply
Lenalidomide: oral tablets or capsules, NHS supply

**Dosage and dose adjustments in line with standard of care. Lenalidomide and dexamethasone dosing can follow frailty adjusted dosing schedules if this is the standard practice at site. In this event the dose selections for lenalidomide and dexamethasone that comply with the dose reductions tables (see Section 19.9) should be followed.*

5. TRIAL FLOWCHART

Figure 1: iFIT trial flowchart



6. PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Table 1: Summary of protocol amendments

PROTOCOL HISTORY	
Amendment	**Date**
Original protocol	<<date>>

This is v1.0 of the protocol. No prior amendments have been made.

III. TRIAL INFORMATION AND STANDARD OF CARE INDUCTION TREATMENT

7. KEY TRIAL CONTACTS

Please direct all trial-specific queries, including clinical queries, to the Coordinating Centre **(CTRU-iFIT@leeds.ac.uk)** in the first instance. Clinical queries will be prioritised by the Coordinating Centre and referred to the Chief Investigators, or delegate, as required.

COORDINATING CENTRE: Clinical Trials Research Unit (CTRU), University of Leeds

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24-hour Registration and Randomisation
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iFIT WEBSITE DETAILS: <<INSERT LINK>>

8. LIST OF ABBREVIATIONS

ADL	Activity of daily living
AE	Adverse event
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
APL	Authorised personnel log
AR	Adverse reaction
ASTCT	American Society for Transplantation and Cellular Therapy
BCMA	B-cell maturation antigen
β2M	Beta 2 microglobulin protein (a tumour marker)
CHI	Community Health Index
CI	Chief Investigator
CIs	Chief Investigator and Co-Chief Investigator
Co-CI	Co-Chief Investigator
CONSORT	The Consolidated Standards of Reporting Trials
CPMS	Central Portfolio Management System
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRP	C-reactive protein
CRS	Cytokine release syndrome
CRUK	Cancer Research United Kingdom
CT	Computed tomography scan
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical trial of investigational medicinal product
CTRU	Clinical Trials Research Unit
CYP	Cytochrome P450 enzyme
Dara-Tal	Daratumamab-Talquetamab
Dara-Tec	Daratumamab-Teclistamab
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic acid
DR	Daratumumab Lenalidomide
DRd	Daratumumab Lenalidomide Dexamethasone
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EFS	Event-free survival
EORTC	European Organisation For Research And Treatment Of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire - Core 30
EORTC QLQ-MY20	EORTC Quality of Life Questionnaire – Myeloma 20
EORTC QLQ-IL	EORTC Quality of Life Questionnaire – Item Library: https://qol.eortc.org/item-library/
EQ-5D-5L	European Quality of Life 5-Dimension 5-Level
FBC	Full blood count
FISH	Fluorescence in situ hybridisation
G8	Frailty screening tool (8 item measure)
GCP	Good Clinical Practice
GCSF	Granulocyte-colony stimulating factor
GDPR	General Data Protection Regulation
GHS	Global Health Status
GP	General Practitioner

H2	Histamine H2 receptor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMDS	Haematological Malignancy Diagnostic Service
HRA	Health Research Authority
IADL	Instrumental activity of daily living
IB	Investigator brochure
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICD	Informed consent document
ICE	Immune effector cell encephalopathy
ICERs	Incremental cost-effectiveness ratios
IgG	Human immunoglobulin G
IMD	Index of multiple deprivation
IMP	Investigational medicinal product
IMWG	International Myeloma Working Group
IRAS	Integrated Research Application System
IRR	Infusion-related reaction
ISF	Investigator site file
ISRCTN	International Standard Randomised Controlled Trial Number
ISS	Integrated summary of safety
ITT	Intention to treat
IV	Intravenous
LCRN	Local Clinical Research Network
LDH	Lactate dehydrogenase
LFT	Liver function test
LICTR	Leeds Institute of Clinical Trials Research
LIMR	Leeds Institute of Medical Research
LP	Lumbar puncture
MA	Marketing authorisation
MACRO	Ennov's MACRO electronic data capture system
MGUS	Monoclonal gammopathy of undetermined significance
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Multiple myeloma
MPT	Melphalan Prednisolone Thalidomide
MR	Minimal response
MRD	Measurable residual disease (positive or negative)
MRI	Magnetic resonance imaging scan
MRP	Myeloma risk profile
NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
NG35	NICE guideline 35
NGF	Next generation flow cytometry
NGS	Next generation sequencing
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
ORR	Overall response rate
OS	Overall survival
PCL	Plasma cell leukaemia
PCR	Polymerase chain reaction
PD	Progressive disease
PET-CT	PET (positron emission tomography) scan with a CT (computed tomography)
PFS	Progression-free survival

PFS2	Progression-free survival (second event)
P-gp	P-glycoprotein
PI	Principal Investigator
PIN	Password identification number
PIS	Participant information sheet
PISICD	Patient information sheet informed consent document
POEMS	Polyneuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes
PP	Per-protocol
PPI	Public and patient involvement
PR	Partial response
PSF	Pharmacy site file
QALY	Quality-adjusted life year
QoL	Quality of life
QP	Qualified person
R&D	Research and development
R2-ISS	Second revision of the international staging system
RBC	Red blood cells
Rd	Lenalidomide dexamethasone
RDE	Remote data entry
REC	Research Ethics Committee
REDCap	Research electronic data capture
R-ISS	Revised international staging system
RMH/ICR	Royal Marsden Hospital/Institute of Cancer Research, London
RNA	Ribonucleic acid
RSAP	Research Staff Advisory Panel
RSI	Reference Safety Information
SAE	Serious adverse event
sAg	Surface antigen
SAP	Statistical analysis plan
SAR	Serious adverse reaction
SC	Subcutaneous
sCR	Stringent complete response
SD	Stable disease
SDV	Source data verification
SFLC	Serum free light chain
SMM	Smouldering multiple myeloma
SmPC	Summary of product characteristics
SOP	Standard operating procedure
SPM	Secondary primary malignancy
SREs	Skeletal-related events
SSOP	Study site operating procedure
STTA	Scale of Subjective Total Taste Acuity
SUAG	Service User Advisory Group
SUSAR	Suspected unexpected serious adverse reaction
TCE	T-cell engager
TMG	Trial Management Group
TMP	Trial monitoring plan
TNE	Transplant ineligible
TP53	Tumour protein 53
TSC	Trial Steering Committee
TTNT	Time to next treatment
TTP	Time to progression
U&E	Urea and electrolytes
UK	United Kingdom

UK-MRA	UK Myeloma Research Alliance
ULN	Upper limit of normal
VEGFA	Vascular endothelial growth factor A
VGPR	Very good partial response
VTE	Venous thromboembolism
WCBP	Women of childbearing potential
ZA	Zoledronic acid

9. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Cancer Research UK	Financial support
Blood Cancer UK	Financial support
Johnson & Johnson Innovative Medicine	Financial support and provision of IMP

10. ROLES & RESPONSIBILITIES

Trial Sponsor – The Sponsor is responsible for trial initiation management and financing of the trial as defined by Directive 2001/20/EC. These responsibilities are delegated to the CTRU as detailed in the trial contract.

Clinical Trials Research Unit (CTRU) – The CTRU will have responsibility for conduct of the trial as delegated by the Sponsor in accordance with relevant Good Clinical Practice (GCP) standards and CTRU Standard Operating Procedures (SOPs). The CTRU will provide set-up and monitoring of trial conduct to CTRU SOPs, and the GCP Conditions and Principles as detailed in the UK Medicines for Human Use (Clinical Trials) Regulations 2004 including but not limited to: randomisation design and service, database development and provision, protocol development, case report form (CRF) design, trial design, source data verification (SDV), monitoring schedule and statistical analysis for the trial. In addition, the CTRU will support submissions for all required approvals, clinical set-up, ongoing management including training, monitoring reports and promotion of the trial. The CTRU will be responsible for the day-to-day running of the trial including trial administration, database administrative functions, data management, safety reporting and all statistical analyses.

Trial Management Group (TMG) – The TMG will comprise the Chief Investigators (CIs), CTRU team, at least one patient contributor/representative from Myeloma UK and other key external member of staff involved in the trial. The TMG will be assigned responsibility for the clinical set-up, on-going management, promotion of the trial, and for the interpretation and publishing of the results. Specifically, the TMG will be responsible for (i) protocol completion, (ii) CRF development, (iii) obtaining required approvals (iv) completing cost estimates and project initiation, (v) nominating members and facilitating the Trial Steering Committee (TSC) and Data Monitoring and Ethics Committee (DMEC), (vi) reporting of serious adverse events, (vii) monitoring of screening, recruitment, treatment, and follow-up procedures, (viii) overseeing consent procedures, data collection, trial end-point validation and database development.

Research Staff Advisory Panel (RSAP) – The RSAP, comprising pharmacists, nurses and other research staff from multiple sites, will provide input to the TMG regarding local processes and the feasibility and practicability of the trial delivery nationwide.

Trial Steering Committee (TSC) – The TSC will provide overall supervision of the trial, in particular trial progress, adherence to protocol, participant safety and consideration of new information. It will include an independent chair, no less than two other independent members and at least one patient contributor. The CIs and other members of the TMG may attend the TSC meetings and present and report trial progress. The Sponsor will also be invited to attend. Detail of membership and functions of the TSC will be agreed and documented in a TSC Charter. The committee will meet annually as a minimum.

Data Monitoring and Ethics Committee (DMEC) – The DMEC will include independent membership and at least one patient contributor. They will review the safety and ethics of the trial by reviewing interim data during recruitment and follow-up. The Committee will meet annually as a minimum. Detail of membership and functions of the DMEC will be agreed and documented in a DMEC Charter. The DMEC will provide their recommendations to the TSC.

Myeloma UK and the Service User Advisory Group (SUAG) – Myeloma UK, a leading patient organisation for myeloma patients in the UK, will co-ordinate a SUAG consisting of patients and carers to provide insights into the project over time. This will be achieved through regular meetings with patients and carers where they will have the opportunity to discuss the design of the research, how the project is progressing, the outcomes of the study and what they mean for myeloma patients.

Myeloma UK will also provide opinion and input into the development of the project, patient dissemination plan, journal articles and other activities that support the research. This is a gold standard approach to Public and Patient Involvement (PPI) that will enable co-creation of the research and ensure it is patient centred. The lead for PPI in Myeloma UK will manage this group, record their activities and views so that they can be evidenced in the dissemination of the results.

Johnson & Johnson Innovative Medicine – Johnson & Johnson Innovative Medicine will have responsibility for the supply of the Investigational Medicinal Products (IMPs) teclistamab, talquetamab, and daratumumab in combination with teclistamab/talquetamab in iFIT1 only.

Clinigen – Clinigen will have responsibility for the distribution of the IMPs teclistamab, talquetamab, and daratumumab in iFIT1 only.

Haematological Malignancy Diagnostic Service, Leeds (HMDS) / Royal Marsden Hospital/Institute of Cancer Research, London (RMH/ICR) / Leeds Institute of Medical Research (LIMR) - The central laboratories are responsible for processing, handling and storing samples and data in accordance with the patient's consent and relevant regulations to provide data relating to trial endpoints or future research.

Chief Investigator (CI) – The CI, along with the co-CI, is involved in the design, conduct, co-ordination and management of the trial. The CI will have joint overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial. Throughout the protocol the CI and Co-CI are referred to as "CIs".

Co-Chief Investigator (co-CI) – The co-CI, along with the CI, is involved in the design, conduct, co-ordination and management of the trial. The co-CI will have joint overall responsibility for the design and set-up of the trial, the investigational drug supply and pharmacovigilance within the trial. Throughout the protocol the CI and Co-CI are referred to as "CIs".

11. PROTOCOL CONTRIBUTORS

This protocol has been reviewed by:

- The key trial contacts (see Section 7), which includes members of the TMG, and
- Research staff at National Health Service (NHS) sites in the RSAP (See Section 10).

The SUAG led by Myeloma UK have contributed to the design of this trial, including Quality of Life (QoL) measures, and the patient-facing documents as detailed in this protocol, including the Participant Information Sheet and Informed Consent Documents (PISICDs).

12. KEY WORDS

Myeloma, Platform adaptive design, Immunotherapy, Frailty, Personalised therapy, Biomarker-driven

13. BACKGROUND AND RATIONALE

iFIT (UK-MRA Myeloma XVIII) is a biomarker-stratified, platform trial addressing the optimal use of immunotherapeutic agents for transplant ineligible (TNE) myeloma patients with a suboptimal response to standard of care induction therapy and addressing treatment duration and de-intensification questions for those with the deepest responses and the frailest patients. Multiple myeloma (MM) is the second most common haematological malignancy with almost 6000 patients diagnosed in the UK each year. MM is predominantly a disease of older people, with two thirds of patients aged over 70 at diagnosis and increasing incidence with population ageing. Treatment approaches for less fit, older patients represent a significant unmet need [2].

The FiTNEss (UK-MRA Myeloma XIV) trial [3], is examining whether frailty-adapted dosing strategies, for the combination ixazomib, lenalidomide and dexamethasone, can improve outcomes for patients compared to the standard "one-size-fits-all" approach of reactive dose modification based on toxicity [4]. In addition, the trial is undertaking a wide range of allied translational/exploratory projects using measurable residual disease assessment (MRD), genetics, digital phenotype MedTech (TRANSFORM sub study) and frailty/senescence biomarkers. FiTNEss has demonstrated that upfront adjustment of dosing, based on International Myeloma Working Group (IMWG) frailty scoring (Functional groups: FIT/UNFIT/FRAIL), can improve outcomes for TNE patients. Although the primary endpoint was not met there was evidence of improvement in early treatment cessation rates for patients in the UNFIT group with prospective dose modification, and in event free-survival (EFS) and overall survival (OS) across the whole trial cohort [5]. Additionally, the lack of significant difference in the FRAIL cohort between prospective and reactive dose modification was likely confounded by very early dose reductions in the reactive group. Overall, the results support the existing evidence of heterogeneity between the different functional patient groups and therefore it follows that subsequent trials should address how to optimise different therapeutic strategies separately for each group separately [6]. Additional priorities considered from conception of the trial design included how to incorporate immunotherapy approaches, that have recently shown dramatic improvements in outcome for patients with relapsed/refractory disease, in earlier lines of therapy and how to address issues of key importance to patients in optimising myeloma treatment delivery. These latter issues were identified using the results of The James Lind Alliance Priority Setting Partnership. This effort resulted in a "Top 10" list of jointly agreed research priorities for patients, caregivers and other stakeholders, published in 2022 [7].

These included: "How can we cure myeloma", "Are novel immunotherapies effective for the treatment of myeloma", "What is the impact of personalised medicine on treatment efficacy and disease outcomes" and "How can we safely reduce, cycle, or stop the use of medications to reduce the side effects of treatment and maintain control over myeloma".

Using these three critical considerations as the basis for iFIT, along with the incorporation of cutting-edge MRD biomarker stratified treatment, has resulted in an innovative, patient-centred, biologically-driven trial design.

The current international standard of care for TNE patients is the triplet daratumumab, lenalidomide and dexamethasone (DRd) which, when given to disease progression, was associated with excellent outcomes in the MAIA trial [8-10]. DRd was approved by the Scottish Medicine Consortium in September 2023 and National Institute for Health and Care Excellence (NICE) in October 2023 and is now the UK standard of care [11]. All patients in the study will therefore commence on treatment with DRd as per standard of care for 6 cycles. MRD analysis of the MAIA trial [12] showed that patients achieving MRD negativity with DRd had the best progression-free survival (PFS) with outcomes suggesting these patients may not need additional therapy upfront to achieve very long periods of remission. In contrast, MRD positive patients relapsed at a median of around 2 years and so have the highest unmet need for further improvement of therapeutic strategies and outcomes. This analysis, in addition to data from our own and other previous studies, cements the role of MRD assessment as a key biomarker of outcome in TNE patients [13, 14] and will be used in the study to drive treatment pathway assignment after DRd induction therapy.

iFIT includes three pathways (**iFIT1/2/3**) aiming to define the optimum treatment strategy for each patient based on response to DRd induction therapy and IMWG frailty subgroup. This approach keeps the James Lind Alliance priority "What is the impact of personalised medicine on treatment efficacy and disease outcomes?" at the heart of the study.

The trial incorporates 3 key clinical questions:

For patients who are MRD positive by flow cytometry (10^{-5}) or have achieved <very good partial response (VGPR) after 6 cycles of DRd induction therapy:

- **iFIT1**: In FIT/UNFIT patients, does escalating to daratumumab combined with T cell engager (TCE) therapy (teclistamab or talquetamab) improve PFS compared to DRd to progression (standard of care)?
- **iFIT2**: In FRAIL patients in whom DRd has not improved frailty status after 6 cycles, does continuing dexamethasone have any additional benefit or could more patients stay on therapy for longer with fewer side effects, if dexamethasone were dropped?

For patients who are MRD negative and ≥ VGPR after 6 cycles of DRd induction:

- **iFIT3**: For all patients MRD negative after DRd induction (regardless of frailty status), can duration of ongoing daratumumab and lenalidomide (DR) therapy be limited to a further 18 months to allow patients a treatment-free interval which is not at the detriment of disease response and participant-reported overall health and QoL?

The background specific to each pathway is included in the individual pathway sections for **iFIT1** (Section 26), **iFIT2** (Section 33), and **iFIT3** (Section 40).

13.1. MRD assessment

MRD assessment is a method of assessing and differentiating the deepest responses to modern myeloma treatment by measuring residual myeloma cells in bone marrow aspirate samples after

treatment. There are currently two widely used methods to assess MRD in myeloma, bone marrow aspirate next generation flow cytometry (NGF) and bone marrow aspirate next generation sequencing (NGS); whilst there are pros and cons to each method, both have been demonstrated to be associated with PFS and OS in transplant eligible and TNE patients. The use of MRD as an endpoint contributing to Food and Drug Administration (FDA) drug approvals has recently been considered and approved although the requirement to continue follow up to confirm PFS and OS remains. Nevertheless, this acceptance will likely enable the accelerated approval of novel therapies for myeloma. The bulk of experience in the UK has used the flow-cytometry based approach and this will be used in iFIT [15].

13.2. Frailty

Within the group of TNE patients there is considerable heterogeneity. This is not well-defined based on age alone, but rather by the complex interplay of age, physical function, cognitive function and comorbidity. Clinician's assessment of patient frailty without formal assessment or "the eyeball test" although quick may lack precision, and more formal methods of assessment have been developed. The IMWG frailty score predicts survival, adverse events (AEs) and treatment tolerability [16]. This score includes the outcome of 3 patient questionnaires, the Katz Activity of Daily Living (ADL) [17], Lawton's Instrumental Activity of Daily Living (IADL) [18] and the Charlson Comorbidity Index [19]. The ADL and IADL scores assess self-care and independence including household tasks. The Charlson Comorbidity Index considers the number and severity of comorbidities. These indices were combined with age in a retrospective study using data from several clinical trials, to define a global frailty score predictive of OS. The IMWG frailty score was subsequently shown to be predictive of both PFS and toxicity. An increase in frailty score was associated with an increased risk of death, progression, non-haematologic AEs and treatment discontinuation that was independent of classical definitions of risk, including International Staging System (ISS) for MM and cytogenetic risk, and also independent of treatment regimen. As such it was suggested to be useful in determining the feasibility of treatment regimens and appropriate dose reductions and this is being validated prospectively in the FiTNEss trial.

The IMWG frailty index relies on subjective assessment of various factors by the clinician and patients. Objective measures of frailty have been proposed including those using blood-based testing and those assessing physical functioning. Several blood-based markers have been associated with adverse outcomes including inflammatory markers such as C-reactive protein (CRP), renal dysfunction, and the ratio of lymphocytes to total white cells (L:W). Using laboratory surrogates that are readily available to measure patient frailty is objective and avoids the need for potentially burdensome questionnaires. Based on our previous studies we have defined a score – The UK-MRA Myeloma Risk Profile (MRP) (see Appendix 48.9) – that combines readily available laboratory measures of patient frailty with age and Eastern Cooperative Oncology Group (ECOG) performance status (PS) to predict outcomes in TNE MM patients [20]. Importantly, it remains prognostic in a subset of patients treated with both immunomodulatory drugs and proteasome inhibitors demonstrating applicability across TNE MM patients treated with different agents.

The IMWG frailty score will be complemented by the G8 frailty screening tool (G8) [21]. The G8 is an 8-item measure that incorporates a greater variety of the domains that may determine risk of frailty (including nutritional status, polypharmacy, mobility), and it is valid in older people with other haematological cancers [22].

Objective measures of physical and cognitive functioning include gait speed (the 4m walk test), and a mini-cog assessment which includes two component parts: a 3-item word recall test and a simple clock drawing test. The mini-cog is a valid and reliable screening tool for detection of clinically significant cognitive impairment [23, 24]. All of these measures can assess function in patients and will be assessed alongside IMWG and UK-MRA MRP in this study.

13.2.1. Qualitative interviews to further understand impact of frailty

Embedded qualitative research within clinical trials is promoted and increasingly valued by regulatory authorities. iFiT offers opportunity to incorporate qualitative research exploring the patient experience of living with or developing frailty during first-line treatment. Funding is being sought for qualitative interviews to collect iFIT participant perspectives. These interviews, carried out at multiple timepoints when frailty is assessed, will contribute richer data to inform understanding of participant experience of living with myeloma and frailty and the impact of early treatment on their lives, as well as contributing to interpretation of objective assessment findings.

13.3. DRd induction therapy

13.3.1. Daratumumab

Daratumumab is a human immunoglobulin IgG1κ monoclonal antibody targeting a cell surface marker on plasma cells, CD38, which is overexpressed on myeloma cells. Cell surface binding leads to both antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity inhibiting growth of myeloma cells and inducing apoptosis [25, 26]. There is also evidence that daratumumab can promote adaptive T cell responses with an increase in T cell proliferation and activation and T cell receptor clonality. CD38+ regulatory T cells are also reduced [27]. CD38 is also expressed, at low level on normal lymphoid and myeloid cells, including myeloid derived suppressor cells and these are reduced after treatment.

The subcutaneous (SC) formulation of daratumumab contains hyaluronidase which depolymerises hyaluronan, a polysaccharide found in the extracellular matrix of SC tissues. This enables the antibody to be taken up through the SC space.

13.3.2. Therapeutic experience of daratumumab

The initial phase 1-2 trial of daratumumab (GEN-501) was conducted in patients with relapsed myeloma with a median of 4 prior lines of therapy. Intravenous (IV) daratumumab demonstrated a response rate of 33% to 36% in this heavily pre-treated population. The estimated median PFS was 5.6 months in the patients receiving 16mg/kg, with an OS rate of 77% at 12 months [28]. This activity was confirmed in the SIRIUS study where all patients received 16mg/kg with a response rate of 29%, median PFS 3.7 months and median duration of response 7.4 months. The 12 month OS rate was 64.8%.

Subsequent trials explored combinations in patients with relapsed and/or refractory myeloma. Daratumumab, lenalidomide and dexamethasone was studied in the POLLUX trial [29]. Daratumumab, lenalidomide and dexamethasone was associated with superior PFS (45.0 vs. 17.5 months; hazard ratio, 0.44; 95% confidence interval, 0.35 to 0.54; $P < 0.0001$) and OS (67.6 vs. 51.8 months; hazard ratio, 0.73; 95% confidence interval, 0.58 to 0.91; $P = 0.0044$) [30] compared to lenalidomide and dexamethasone alone. Common grade 3 and 4 toxicities included neutropenia (57.6% vs. 41.6%), anaemia (19.8% vs. 22.4%), thrombocytopenia (15.5% vs. 15.7%), pneumonia (17.3% vs. 11.0%) and diarrhoea (10.2% vs. 3.9%).

The MAIA study [8] studied this comparison in newly diagnosed patients not eligible for stem cell transplant. Patients in the daratumumab group received IV daratumumab 16mg/kg once weekly for 8 weeks, every 2 weeks during cycles 3 through 6, and every 4 weeks thereafter. Lenalidomide was given orally at 25mg for 21 out of 28 days and dexamethasone at 40mg weekly, reduced to 20mg weekly for those aged over 75 years. Treatment was continued to progression or intolerable side effects. At 64.5 months median follow up PFS was improved with DRd versus lenalidomide and dexamethasone (Rd) (median, 61.9 vs. 34.4 months; hazard ratio 0.55; 95% confidence interval, 0.45 to 0.67; $P < 0.0001$)

[31]. Median OS was not reached with D-Rd versus 65.5 months with Rd (hazard ratio, 0.66; 95% confidence interval, 0.53 to 0.83; P = 0.0003), with estimated 60-month OS rates of 66.6% and 53.6%, respectively. Grade 3 or 4 adverse events seen with DRd included neutropenia (54.1%), anaemia (17.0%) and pneumonia (19.5%).

Detailed MRD analysis of the MAIA trial was presented along with data from the ALCYONE trial which studied the addition of daratumumab to the bortezomib, cyclophosphamide and dexamethasone backbone. Patients achieving MRD negativity achieved significantly longer median PFS than those who did not, and the rates of MRD negativity were higher with the addition of daratumumab in both studies [12]. Sustained MRD negativity at 6 and 12 months was associated with improved outcomes compared to single timepoint assessment. Patients in the MAIA trial achieving MRD negativity had a very low rate of progression (<20% at 3 years) raising the question of whether treatment needs to be continued indefinitely in this group.

Benefit from the addition of daratumumab to the lenalidomide and dexamethasone backbone was seen across all frailty subgroups using the abbreviated frailty score (substituting ECOG PS for the IADL and ADL questionnaires) [9].

The COLUMBA study compared IV to SC daratumumab and demonstrated similar efficacy (objective response rate (ORR) 39.8% vs. 43.7%, PFS 6.1 vs. 5.6 months, OS 25.6 vs. 28.2 months, for IV vs. SC, respectively) but with fewer IRRs (34.5% vs. 12.7%) [32]. SC daratumumab is therefore now the standard of care and will be used in this study.

Recent data from trials in TNE (or transplant deferred) patient groups studying the combination of daratumumab (and the other anti-CD38 antibody, isatuximab) with lenalidomide dexamethasone and a proteosome inhibitor have been recently reported [33, 34]. These combinations are not yet reimbursed by NICE, or other agencies, in the UK.

13.3.3. Daratumumab dose rationale

The standard recommended dose of 1,800mg of daratumumab solution for SC injection administered over approximately 3 to 5 minutes will be used according to the following dosing schedule during the induction phase of the trial:

Cycle 1 to 2: weekly (total 8 doses).

Cycle 3 to 6: every two weeks (total 8 doses).

The dose of daratumumab should not be modified based on frailty.

13.3.4. Lenalidomide

Lenalidomide binds directly to cereblon, a component of a cullin ring E3 ubiquitin ligase enzyme complex that includes deoxyribonucleic acid (DNA) damage-binding protein 1(DDB1), cullin 4 (CUL4), and regulator of cullins 1 (Roc1). In the presence of lenalidomide, cereblon binds substrate proteins Aiolos and Ikaros which are key myeloma transcription factors, leading to their ubiquitination and subsequent degradation resulting in cytotoxic and immunomodulatory effects.

13.3.5. Therapeutic experience of lenalidomide

Lenalidomide is a thalidomide derivative and immunomodulatory agent available as an oral preparation, which is more potent in *in vitro* assays and with a different adverse effect profile than thalidomide. It is administrated daily for 21 days of a 28-day cycle, usually with dexamethasone also given during the treatment course.

Lenalidomide was first shown to be effective in the treatment of myeloma at relapse in two large phase III studies in Europe and the United States using the same protocol (lenalidomide/dexamethasone vs. dexamethasone) [35, 36]. These trials showed similar results confirming the superiority of the combination lenalidomide plus dexamethasone to dexamethasone alone both in terms of response (complete response (CR) 15% vs. 2%, ORR 60% vs. 22%) and survival (PFS 11.1 months vs. 4.7 months, OS 29.6 months vs. 20.2 months). A major benefit of lenalidomide is the absence of associated neurotoxicity or sedation seen with thalidomide, making it more tolerable; however, there is a significant rate of myelosuppression (20%), which is not seen with thalidomide. The rates of venous thromboembolism (VTE) are similar with both agents.

At diagnosis in TNE patients:

The FIRST/MM-020 trial demonstrated improved outcomes, including QoL [37], with the newer generation immunomodulatory drug lenalidomide, continued to disease progression, over other treatment strategies [38]. The PFS was 25.5 months with continuous Rd, 20.7 months with Rd for 18 cycles (72 weeks, Rd18) and 21.2 months with melphalan, prednisolone and thalidomide (MPT) for 72 weeks. The hazard ratio for the risk of progression or death was 0.72 for continuous Rd versus MPT and 0.70 for continuous Rd versus 18 cycles of Rd ($P < 0.001$ for both comparisons). An updated analysis of OS showed a median survival of 58.9 months with Rd, 56.7 months with Rd18, and 48.5 months with MPT [39]. This has now been improved with the addition of daratumumab to the lenalidomide/dexamethasone backbone as described above.

13.3.6. Lenalidomide dose rationale

The standard dose of lenalidomide, 25mg given 21 days out of 28, was established in the pivotal MM009 and MM010 studies [40] and used in the MAIA study of DRd. However, in all these studies toxicities were seen at a higher rate in older patients [9]. A study enrolling relapsed MM patients at higher risk of myelosuppression, due to age or renal impairment, examined a dose of 15mg lenalidomide (days 1 to 21/28) and found no difference in response rate or PFS to that seen in MM009/MM010 [41]. Multiple international guidelines [42] support the use of frailty adapted dosing for older myeloma patients and although it did not meet its primary endpoint, data from FiTNEss also supports consideration of this approach. Dosing of lenalidomide within the study can therefore follow local standard of care as long as the maximum recommended dose of 25mg is not exceeded.

13.3.7. Dexamethasone

Dexamethasone is a synthetic corticosteroid at least 25 times more potent than native cortisol. Dexamethasone has been shown to induce apoptosis via termination of RAS/RAF signalling (Rat sarcoma/rapidly accelerated fibrosarcoma - a signal transduction pathway), inhibition of nuclear factor kappa B (NF-kB) which leads to the reduction in expression of IL-6 and suppression of the anti-apoptotic factors, EIF2 and mTOR, along with other mechanisms [43].

13.3.8. Therapeutic experience of dexamethasone

Corticosteroids are very active against myeloma without myelotoxicity. However, they do have a variety of other side effects such as hypertension, hyperglycaemia, gastritis, weight gain, fluid retention, mood swings, opportunistic infections, insomnia, osteopenia and Cushing syndrome, some of which are more pronounced in older patients. In all patients the standard of care for dexamethasone dosing has reduced from schedules involving 40mg for 4 day pulses every two weeks to giving one dose weekly (of 40mg in younger fitter patients) following the findings of a study

demonstrating superior OS and lower toxicity at these doses [44]. Further dose reductions to 20mg are universally recommended for patients aged over 75 years.

13.3.9. Dexamethasone dose rationale

Based on the same arguments as for lenalidomide, dexamethasone dosing should follow local standard of care but should not exceed the recommended dosing with the label for DRd (40mg/week for those aged ≤75 years and 20mg/week for patients ≥76 years. Age should be defined at cycle 1 day 1 and dosing should not alter due to a subsequent birthday.

13.4. Cytogenetic and other risk assessment

The ISS for MM predated routine cytogenetic assessment and combines measurement of Beta 2 microglobulin protein (β_2M) and albumin. Three groups were defined, I (β_2M < 3.5mg/L, albumin ≥ 35g/L), II (not I or III) and III (β_2M ≥ 5.5mg/L) [45]. Advances in our understanding of the molecular evolution of myeloma led to additional cytogenetic changes being recognised as contributing to outcome prediction. Cytogenetic changes occur at myeloma initiation but can also be acquired at times of disease progression or recurrence. Certain changes are associated with shorter PFS and OS [46]. These include the commonly assessed translocations t(4;14), t(14;16), t(14;20), copy number changes del(17p) and gain(1q) and mutations of the tumour protein 53 (TP53) gene. Cytogenetic risk has been shown in previous studies to contribute less to the outcome of TNE patients than that of those younger and fitter but still has an impact on outcome. These changes have been combined into a number of different staging systems evolving over time. The R-ISS defines 3 groups and combines ISS with the cytogenetic changes del(17p), t(4;14) and t(14;16) and lactate dehydrogenase (LDH). The R2-ISS defines 4 groups and incorporates gain(1q), del(17p) and t(4;14) as well as assigning different weights to different features [47]. A new risk classification is expected to be published in 2025 and will include mutations in the TP53 gene in addition to the features mentioned above.

In England, NICE guideline [NG35] (published 10 February 2016, updated 25 October 2018) recommends performing fluorescence in-situ hybridisation (FISH) on CD138-selected bone marrow plasma cells to identify the adverse risk abnormalities t(4;14), t(14;16), gain(1q), del(1p) and del(17p) in all newly diagnosed patients. It also recommends using these abnormalities alongside ISS scores to identify people with high-risk myeloma. More recently sequencing of TP53 became available routinely via NHS Genomic Laboratory Hubs for all NDMM patients.

13.5. Quality of life and cost-effectiveness

QoL data supplements efficacy assessments in clinic to gain a deeper understanding of the impact of a treatment or therapeutic strategy on participants daily lives. To facilitate the analysis of the outcomes data and expedite its transfer to general UK clinical practice, QoL and cost-effectiveness data will be collected in accordance with the NICE technology appraisal reference case [48]. The following measures will be collected [49]:

- EQ-5D-5L,
- EORTC QLQ-C30,
- EORTC QLQ-MY20,
- EORTC QLQ-IL413,
- EORTC QLQ-IL414 (after 6 cycles of standard of care induction treatment and **iFIT1** participants only), and
- Healthcare Resource Use.

The EQ-5D-5L questionnaire [50], captures a generic measure of QoL required for NICE appraisals as it allows comparisons across disease areas, necessary for reimbursement decisions. The EORTC QLQ-C30 [1] and QLQ-MY20 [51] questionnaires capture disease-specific measures of QoL and may be more sensitive to disease specific impacts than generic measures of QoL. The EORTC QLQ-IL413 [49] is a subset of questions, equivalent to the EORTC QLQ-SS136 infection symptom scale, which focus on the patient experience of infections during a cancer diagnosis, a known risk associated with receiving TCE therapy [49]. The EORTC QLQ-IL414 questionnaire [49] captures measures on oral health; this is a subset of items from the EORTC QLQ-OH15 questionnaire [52] and will record the impact of the TCEs, especially the common oral side-effects of talquetamab. The health care resource use questionnaire captures patient use of healthcare services and, in combination with effectiveness and QoL information, facilitates cost-effectiveness estimates needed for NICE re-imbursement assessments.

EORTC QLQ-IL413 and EORTC QLQ-IL414 questionnaires can be accessed via the item library (https://qol.eortc.org/item-library/).

13.6. Bone disease and therapy

Zoledronic acid (ZA) is an established component of modern myeloma therapy, on the basis that it reduces both skeletal-related events (SREs), including vertebral fractures, and improves OS, compared to oral sodium clodronate, as demonstrated by the Myeloma IX study [53]. Within that trial, ZA was administered 4-weekly from diagnosis, continuing indefinitely, with differences in outcome still evident after at least 2 years of therapy; on this basis current IMWG guidelines recommend monthly treatment for 2 years from diagnosis.

Subsequently Raje *et al.* compared denosumab to ZA [54]. This study demonstrated a reduction in SREs associated with denosumab. Denosumab can also be used in patients with significant renal impairment, though due to the absence of national commissioning, a recent survey of UK practice indicated fewer than half of centres are able to access this therapy (Choudhuri et al., manuscript in preparation).

Although these trials represent a randomised controlled trial evidence base, since their publication many aspects of myeloma therapy have evolved; in particular, depth and duration of response have improved markedly, which may improve bone outcomes irrespective of specific bone-directed therapy. Additionally, bisphosphonates and denosumab are not harmless drugs, being associated with a significant risk of side effects including osteonecrosis of the jaw, acute kidney injury, resistance hypocalcaemia, acute phase reactions and exacerbation of bone pain, and conferring a significant logistic treatment burden for patients. Against this background, UK and global practices have understandably become heterogeneous with respect to bone-directed therapy. For example, a recent UK survey of practice (Choudhuri *et al.*, manuscript in preparation) indicated 76% of responding clinicians stopped monthly ZA after 2 years, and 54% considered escalation or de-escalation of bone therapy after 12 months.

Modern myeloma treatment now raises several new clinical questions which require appraisal, for example concerning optimal dosing frequency, duration of therapy, and identification of groups that may benefit from more or less intense bone therapy regimens. The recruitment of a large, clinically well-characterised and homogeneously treated cohort of patients within the iFIT study provides an opportunity to understand and assess bone- and disease-related outcomes with respect to standard of care bone therapy.

13.7. Risk of infections

Identifying and managing infective complications seen in myeloma patients is an integral component of successfully treating the disease. This can be most problematic in the newly diagnosed patient population where the early mortality (death within 6 months of treatment initiation) attributed to infection has been reported in up to 4.5% of trial patients [55] with real world data suggesting that over 20% of deaths within 1 year of diagnosis are due to infection [56]. In particular NDMM patients have a 7-fold increased risk of bacterial infections and a 10-fold increased risk of viral infections [56].

Such increased risk can, in part, be attributed to the inherent immunosuppressive nature of a plasma cell malignancy. Factors contributing to this immunosuppressive environment include B cell dysfunction and hypogammaglobulinaemia, dendritic cell dysfunction and impaired antigen expression, natural killer cell depletion and dysfunction, T cell exhaustion and senescence, treatment related neutropenia and increased immunosuppressive cells such a myeloid derived suppressor cells [57-64]. This can result in secondary immunodeficiency which is independently associated with inferior OS [65].

DRd has been proven to induce durable remissions in the phase III MAIA study, which compared DRd to Rd in newly diagnosed TNE myeloma [10]. The 5-year PFS and 7-year OS were 52.1% and 53.1%, respectively, in the DRd arm versus 29.6% and 39.3%, respectively, in the Rd arm [66]. Grade 3 or more infections were reported in 41% of the DRd group with the most common infective complication being pneumonia, which was seen in 30% [67]. This was reported as grade 1-2 in 11%, grade 3 in 17%, and grade 4 in 1% with 3 patients (1%) dying from this complication. Other opportunistic infections included oral candidiasis, herpes zoster, oral fungal infection, oesophageal candidiasis, and pneumocystis jirovecii pneumonia [67]. All grade infections, such as bronchitis was also reported in 34%, upper respiratory tract infections in 26%, whilst 61% of patients experienced neutropenia and 19% experienced lymphopenia [67].

We will collate the incidence of infective episodes during DRd therapy and following randomisation. We will also collect participant experience of infections through a validated patient reported outcome measure. Through exploratory analysis we will investigate the possible correlation of infective episodes reported during DRd treatment, and those subsequently reported following randomisation to determine if there are disease- or patient-related factors that may enable prospective identification of patients at risk of infection, particularly those who are exposed to bi-specific antibody therapy during enrolment in iFIT1 (see Section 26.1).

14. OBJECTIVES AND ENDPOINTS

14.1. Objectives

The majority of objectives and endpoints are defined according to randomisation pathway. Refer to the individual pathway sections for **iFIT1** (Section 27), **iFIT2** (Section 34), and **iFIT3** (Section 41). However, there are some secondary and exploratory objectives which consider treatment during standard of care induction and crosscut the iFIT randomisation pathways. These, along with their associated endpoints are defined here for completeness.

14.1.1. Secondary objectives

The standard of care induction secondary objectives are to assess the following endpoints during DRd induction therapy:

1. Overall response rate (ORR),
2. Attainment of ≥VGPR,
3. Attainment of MRD negativity,
4. Treatment compliance,
5. Toxicity and safety,
6. Incidence of secondary primary malignancies (SPMs),
7. Incidence, rate and type of infections,
8. Quality of life (QoL),
9. Objective measures of function, and
10. Cost-utility.

The cross-cutting secondary objectives are to assess the following endpoints throughout the trial, including during DRd induction therapy and into each iFIT pathways:

1. Survival after progression, and
2. Time to next treatment (TTNT).

These endpoints will be considered both per iFIT pathway (if applicable) and overall.

14.1.2. Exploratory objectives

The exploratory objectives throughout the trial, including during DRd induction therapy and crosscutting all iFIT pathways, are:

1. To perform an investigation into bone disease and therapy: observe and understand current UK bone therapy practice and investigate how it impacts on various bone and clinical myeloma outcomes, in order to generate hypotheses to inform future research in this area.

14.1.3. Translational objectives

The translational objectives throughout the trial, including during DRd induction therapy and crosscutting all iFIT pathways, are:

1. To collect patient samples at key timepoints to enable the delivery of key translational endpoints (see Section 14.2.3).

14.2. Endpoints

14.2.1. Secondary endpoints

Overall response rate (ORR)
The categorical response to treatment at the end of DRd induction therapy: stringent complete response (sCR), CR, VGPR, PR, minimal response (MR), stable disease (SD), or Progressive Disease (PD).

Attainment of ≥VGPR
The binary response to treatment at the end of DRd induction therapy when ORR is dichotomised as ≥VGPR (sCR, CR, VGPR) versus <VGPR (PR, MR, SD, PD).

Attainment of MRD negativity
The binary MRD status, negative versus positive, at the end of DRd induction therapy as assessed by flow cytometry; MRD negativity is defined as at least a serological VGPR and MRD negative bone marrow aspirate at the 10^{-5} threshold.

Treatment compliance

Compliance with DRd induction therapy is defined in multiple ways: a binary variable indicating whether all cycles of treatment were completed, the number of cycles completed, and the total dose of each trial medication received. The number and causes of dose omissions, dose delays, and dose reductions will also be reported, by trial medicinal product.

Toxicity and safety
All adverse events (AEs), adverse reactions (ARs), serious adverse events (SAEs), serious adverse reactions (SARs), and suspected unexpected serious adverse reactions (SUSARs) reported during DRd induction therapy, as graded by NCI-CTCAE V5. Also included are the numbers of pregnancies in both trial participants and their partners where appropriate.

Incidence of secondary primary malignancies (SPMs)
The number and details of all other cancers, defined as SPMs, reported during DRd induction therapy.

Incidence, rate, and type of infection
In the first instance, this is defined as the proportion of participants experiencing an infection of any type or grade, as graded by NCI-CTCAE V5, during DRd induction therapy. Rate of infection is the number of infections experienced divided by the total number of participant days during DRd induction therapy. This will then be extended to consider grade 3, 4, and 5 infections only and then each type of infection (e.g., fungal, viral, bacterial) separately.

Quality of life (QoL)
Health-related QoL, as scored using the following participant reported questionnaires: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-MY20. Participant-reported infections will be assessed using the EORTC QLQ-IL413. QoL questionnaires will be completed at the start and end of DRd induction therapy.

Objective measures of function
Objective measures of function as measured using the 4 meter walk test and mini-cog assessments, carried out at the start of, after 3 cycles, and at the end of DRd induction therapy.

Cost-utility
Cost-utility will be assessed using costs, quality-adjusted life-years (QALYs) and net health benefit. Costs will be estimated per participant, accounting for therapy costs and healthcare resource use. QALYs are estimated by quality-adjusted survival using the EQ-5D-5L. NHB is defined as QALYs – (costs / £20,000), where £20,000 represents the willingness to pay threshold per QALY.

Survival after progression
The time from first documented evidence of disease progression to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive. This endpoint is only defined for those who experience progression.

Time to next treatment (TTNT)
The time from the date of registration to the date of commencement of next line treatment (i.e., treatment following documented evidence of disease progression). Participants who do not receive next line treatment will be censored at the date of the last assessment or follow-up visit where they are known to have received no new therapy.

14.2.2. Exploratory endpoints

Investigation into bone disease and therapy
In the first instance, this is defined as a series of categorical outcomes derived using the information collected at trial entry and during trial treatment:

- Bone therapy planned and prescribed,

- Dental assessment received during the trial, and
- Bone disease (including SREs) experienced during the trial.

Further explicit derivation of this endpoint will be included in the statistical analysis plan (SAP) and may consider time to first bone therapy.

14.2.3. Translational endpoints

Translational analysis plans will be written by the relevant laboratories. Endpoints will include, but not be limited to, the following:

1. Host biology, and
2. Tumour biology and response.

15. TRIAL DESIGN

iFIT is a multi-centre, open-label, phase III platform trial with three randomised-controlled parallel-group components of TNE patients with newly diagnosed multiple myeloma (NDMM). The trial plans to recruit 1226 participants over a four-year period to reach the required sample size for each of the components. Patients will enrol at the time of diagnosis and complete six cycles of induction DRd before the randomised phase of the trial. They will undergo response assessment, MRD bone marrow assessment and frailty assessment as per IMWG criteria [16] at this time, which will be used to assign their treatment pathway. Participants who are MRD positive and FIT or UNFIT will be assigned to **iFIT1**. Participants who are MRD positive and FRAIL will be assigned to **iFIT2**. Participants who are MRD negative will be assigned to **iFIT3**. Following assignment, participants will be assessed for eligibility to enter their assigned pathway.

The design of each pathway is included in the individual pathway sections for **iFIT1** (Section 28), **iFIT2** (Section 35), and **iFIT3** (Section 42).

16. TRIAL SETTING

Research sites will be identified via a feasibility assessment to determine those most appropriate to participate in the trial. The NHS DigiTrials Feasibility Self-Service will be used to inform research site selection.

Research sites will be required to confirm capacity and capability and undertake site initiation training with the CTRU prior to the start of recruitment into the trial. Each research site will also be asked to complete an Authorised Personnel Log (APL) detailing all staff members who will be involved in the trial at the research site, and the number of years since they commenced their haematology training, if willing to provide. We will collect this to compare clinical assessments of frailty.

Screening and recruitment processes must not be initiated at site until approval to open to recruitment has been formally issued by the CTRU.

1226 participants will be registered into the trial from multiple research sites from around the United Kingdom over a 48-month period. The majority of potential participants will be identified by the patient's existing clinical care team at the time they are referred to the haematology outpatient department with suspected MM. A smaller number of participants may be identified during inpatient admissions.

Invitation to participate in the trial and provision of information will be made either during their first consultation, when routine diagnostic tests will be performed and potential treatment options discussed, or at the time they receive their diagnostic test results.

A list of the research sites can be found on the iFIT website (see Section 7).

17. PARTICIPANT ELIGIBILITY

Eligibility waivers to inclusion/exclusion criteria are not permitted.

Confirmation of eligibility for the trial must be recorded in the patient's notes.

17.1. Trial registration

Patients must meet all of the following inclusion criteria and none of the exclusion criteria.

Of note the eligibility for the overall protocol, and **iFIT2** and **iFIT3** pathways have been kept deliberately very permissive as patients will receive standard of care treatment only. Not all patients eligible at registration will be eligible to proceed to **iFIT1** if assigned to that pathway as additional eligibility criteria are in place for **iFIT1** for safety reasons. Nevertheless, we encourage research sites to recruit all patients eligible at the registration phase as it cannot be predicted whether the patient in question will be assigned to **iFIT1** or not at that time. Registered patients who are assigned to **iFIT1** and not eligible to proceed will continue with standard of care treatment off-trial.

Each patient must only be registered once.

17.1.1. Inclusion criteria for registration

1. Newly diagnosed as having symptomatic MM, plasma cell leukaemia or non-secretory MM according to IMWG diagnostic criteria 2014 (see Appendix 48.1).
   Urine/serum measurable myeloma:
   a. Paraprotein ≥ 10g/L, AND/OR
   b. Urine monoclonal protein (Bence Jones Protein) ≥ 200mg/24hr,
   OR Light chain only myeloma:
   c. Serum free light chains (SFLC) ≥100mg/L with abnormal ratio,
   OR Oligo/Non-secretory myeloma (not meeting any of the above):
   d. ≥ 30% neoplastic plasma cells in bone marrow,
2. Considered not suitable to receive autologous stem cell transplant as part of their first line therapy by the treating clinician,
3. Planned for treatment with Daratumumab, Lenalidomide and dexamethasone (DRd) as first line therapy as standard of care,
4. Aged 18 years or greater,
5. Able to provide full informed consent, and
6. Prepared to comply with pregnancy prevention plan.

17.1.2. Exclusion criteria for registration

1. Smouldering myeloma (SMM), primary amyloidosis, solitary plasmacytoma of bone or extramedullary plasmacytoma (without additional evidence of myeloma),
2. Pregnant, breastfeeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within 3 months after the last dose,

3. Previous treatment for myeloma, except the following:
   a) local radiotherapy to relieve bone pain, spinal cord compression or directed at an anatomically threatening lesion,
   b) bisphosphonate or other bone directed treatment, or
   c) systemic corticosteroids where the total dose received is equal to or less than 160mg dexamethasone (or equivalent). Prior steroid treatment for other co-morbid conditions is allowed as long as it does not exceed 160mg of dexamethasone within the month prior to cycle 1, day 1 on trial,
4. Active systemic viral, fungal or bacterial infection requiring systemic therapy. Criteria for specific chronic infections clarified below:
   a. Participants with human immunodeficiency virus (HIV) can participate after discussion with the CIs unless they meet the following criteria:
      i. History of AIDS-defining illness,
      ii. CD4 count <350 cells/mm3 at screening,
      iii. Detectable viral load during screening or within 6 months prior to screening,
      iv. Not receiving ART,
      v. Had a change in antiretroviral therapy within 6 months, or
      vi. Receiving antiretroviral therapy that may interfere with study drugs.
   b. Participants with evidence of hepatitis B infection AND hepatitis B surface antigen (sAg) or hepatitis B virus (HBV)-DNA positive at the time of screening. Participants with hepatitis B core antibody positivity must undergo HBV-DNA testing,
   c. Active hepatitis C as measured by positive hepatitis C virus (HCV) RNA. Participants with a history of HCV antibody positive must undergo HCV-RNA testing. If a participant has prior Hepatitis C and has completed antiviral therapy and has undetectable HCV-RNA ≥12 weeks following the completion of therapy they are eligible, or
5. Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring.

17.2. Trial randomisation

For entry into each of the randomisation pathways, participants must have completed 6 cycles of standard of care induction therapy with at least a partial response (PR) and have an MRD result. Further eligibility criteria for each pathway is included in the individual pathway sections for **iFIT1** (Section 29), **iFIT2** (Section 36) and **iFIT3** (Section 43).

18. TRIAL PROCEDURES

18.1. Responsibility for information provision, informed consent and eligibility assessments

Provision of information about the trial is permitted by any member of the research site team approved to do so by the Principal Investigator (PI) as detailed on the trial APL.

Full informed consent must be obtained by, and the ICD signed by a medically qualified member of the research site team (QP), approved to do so by the PI as detailed on the trial APL. Consent for bone marrow sample only is permitted to be taken by any member of the research site team approved to do so by the PI as detailed on the trial APL.

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any medically QP delegated responsibility (or other research site team member for bone marrow consent) to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki 1996. Full informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are out-with standard routine care at the research site (including disclosure of confidential patient information to anyone outside of the patients' usual care team).

Participants able to sign or make a mark on the ICD will do so. Where a participant is unable to sign or make a mark, they will be asked to indicate their consent verbally in the presence of a witness (an individual other than a member of the research site team) who is present during the entire informed consent discussion. The witness subsequently signs the ICD to confirm that the information in the PISICD, and any other written information, was accurately explained to and was apparently understood by the participant, and that the participant has given their verbal consent.

The use of an interpreter or translator during the informed consent discussion is at the discretion of the research site. Where an interpreter or translator is used, this must be stated in the patient's notes.

The right of a participant to refuse participation at any stage without giving reasons must be respected. The participant must remain free to withdraw their consent to participate in the trial at any time without having to give reasons and without prejudicing their further treatment. They must also be provided with a contact point where they may obtain further information about the trial (see Section 18.19). Where a participant is required to re-consent or new information is required to be provided to a participant, it is the responsibility of the PI to ensure this is done in a timely manner and according to any timelines requested by the CTRU.

A record of the consent process for the bone marrow consent (see Section 18.5.1), trial registration (Section 18.7.1) and consent to pathway randomisation (see **iFIT1** Section 30.3.1, **iFIT2** Section 37.3.1, **iFIT3** Section 44.3.1) will be kept in the participant's notes. This will include the date of consent and all those present. For each consent, the original consent document will be filed in the Investigator Site File (ISF), a copy of the fully completed ICD will be given to the participant, and a copy will be returned to the CTRU.

Eligibility according to the trial protocol must be confirmed prior to trial registration (see Section 17.1) and entry into the randomisation pathway (see **iFIT1** Section 29, **iFIT2** Section 36, **iFIT3** Section 43) by an appropriately medically trained delegate as detailed on the trial APL. Eligibility for the trial will be recorded in the participant's notes and on the relevant electronic case report form (eCRF). The statement in the notes should be similar to "This patient meets all of the inclusion criteria and none of the exclusion criteria and is therefore eligible for entry onto the iFIT trial **OR** eligible for continuing their participation into the **iFIT1** or **iFIT2** or **iFIT3** pathway". The statement in the notes can be made by any healthcare professional (e.g., a research nurse) if it is made clear that a medically qualified doctor made the decision.

18.2. Non-iFIT registration

Each research site will be required to complete a non-iFIT registration eCRF of all patients with NDMM who are TNE and initiate combination therapy with daratumumab, lenalidomide and dexamethasone (DRd), but are not entered into the trial either because they are ineligible or because they decline participation. This eCRF should not include patients who are registered/randomised for either bone marrow (see Section 18.5), trial registration (see Section 18.7) or entry into the randomisation pathway (see **iFIT1** Section 30.3, **iFIT2** Section 37.3, **iFIT3** Section 44.3).

Anonymised information will be collected including:

- Age,
- Sex,
- Ethnicity, and
- Reason for ineligibility for trial participation/reason for declining participation.

Each individual should only be recorded as a non-iFIT registration once. Reasons for non-iFIT registration will be monitored by the CTRU alongside recruitment progress.

18.3. Trial registration system

Bone marrow registration and trial registration will be performed centrally using the CTRU automated 24-hour web-based system. An authorised PIN will be required for first time users to access the system. They will be provided by the CTRU to staff approved to use the system by the PI on the trial APL, after the research site has received formal approval to open to recruitment. Existing users will access the system using their email and personal password. All registrations and randomisations can be accessed using the following link: https://lictr.leeds.ac.uk/webrand/.

Care must be taken to ensure the correct "service" (iFIT trial), "event" (bone marrow registration **or** trial registration) and site code are selected/entered to ensure correct registration.

18.4. Risk stratification

Bone marrow samples will be analysed at time of diagnosis at local cytogenetics laboratories for high-risk markers as standard of care (see Section 18.5.1 for information regarding consent for analysis of the diagnostic sample at trial central laboratories). The test used to identify the high-risk markers will be in line with local standard of care (e.g., FISH or multiplex ligation-dependent probe amplification). Risk status based on the second revision of the ISS (R2-ISS) stage (Stage I, Stage II, Stage III, or Stage IV; see Appendix 48.8) is required for stratification at randomisation.

Original/copy reports of the genetic testing results should be sent to the CTRU where they will be reviewed by the CI/TMG delegates for risk stratification. Each adverse lesion will be recorded as "present", "absent", "not tested" or "failed" in order to generate the overall risk status alongside other components of the R2-ISS. Genetic test results sent to the CTRU should only include trial number, initials, and date of birth to identify the participant. Risk status will then be updated on Ennov's MACRO electronic data capture system (MACRO) by the CTRU prior to the participant ending standard of care induction.

If the genetic test report shows a full test failure, i.e., no information relating to adverse lesions is available, a second bone marrow collection is not required but a copy of the unsuccessful genetic test report should be sent to the CTRU. If partial results are obtained from the genetic analysis, it is possible that the CTRU will be able to determine risk status. Therefore, reports showing partial results should still be forwarded to the CTRU.

If risk status cannot be determined, participants can continue on the trial. Note this may result in their high-risk R2-ISS stage stratification factor being "Unknown" at randomisation. This classification must be confirmed by CTRU.

18.5. Bone marrow samples at the time of routine diagnostic investigations

18.5.1. Consent for bone marrow samples

At the time of routine diagnostic investigations (when a myeloma diagnosis is not yet confirmed) potential trial participants will be asked to consent to a sample of their bone marrow being sent to the trial central laboratories, to avoid the need for repeat bone marrow sampling on entry to the trial.

Potential trial participants will be provided with a verbal explanation and a short-written Bone Marrow Sharing PISICD. The patient will have the opportunity to ask any questions. The PIS describes what will happen to the samples taken and provides brief information about the trial. If feasible, patients will be given at least 24 hours to consider this information before being asked to give full informed consent. However, given the standard care nature of the investigations, they may be asked to give full informed consent using the Bone Marrow Sharing ICD at the time of discussion with the clinical care team, if the clinical care team is satisfied that the patient understands the nature of the request and its implications. The right of a participant to refuse for samples to be sent without giving reasons must be respected.

The following consent items will be optional:

- Consent for samples to be used in future research:
    - If diagnosed with a plasma cell dyscrasia* other than myeloma, or
    - If diagnosed with myeloma and does not come to take part in iFIT.

*Plasma cell dyscrasias such as Monoclonal Gammopathy of Undetermined Significance (MGUS), Smouldering Multiple Myeloma (SMM), Systemic Amyloidosis, POEMS syndrome and solitary plasmacytoma.

18.5.2. Bone marrow registration

Full informed consent for the bone marrow sample must be obtained prior to bone marrow registration.

Once full informed consent for the bone marrow sample has been obtained, the patient's details must be registered with the CTRU by any authorised member of staff at the research site. The patient will be allocated a bone marrow number upon registration. Bone marrow consent and bone marrow registration do not have to be performed on the same day.

The following information will be required at bone marrow registration:

- Research site name and site code,
- Patient details, including initials, date of birth, sex and NHS/CHI number,
- Confirmation of full informed consent for bone marrow sample, and
- Confirmation of decision regarding optional consent items (Section 18.5.1).

Care must be taken to ensure the correct "service" (iFIT trial), "event" (bone marrow registration) and site code are selected/entered to ensure correct registration.

24-hour bone marrow registration:

https://lictr.leeds.ac.uk/webrand/

Following registration, completed Bone Marrow Sharing consent documents must be sent via the CTRU Secure File Transfer Service or other CTRU-approved method (never standard e-mail).

Automated confirmation of bone marrow registration will be emailed to the research site team.

18.5.3. Sending the bone marrow samples

The samples will be sent to local laboratories for genetic testing as per local protocol. In addition to this, the samples should be sent to the central laboratories (see Appendices 48.6.3 and 48.7):

- HMDS: Bone marrow aspirate (5mL) in ethylenediaminetetraacetic acid (EDTA), and
- RMH/ICR: Bone marrow aspirate (5mL) in EDTA.

The samples must be labelled with bone marrow ID number (site code/*****), participant NHS/CHI number, initials, sex and date of birth. The bone marrow sample sent to HMDS **only** should also include the participant's full name.

18.5.4. Patients who do not proceed to trial registration or are diagnosed with other plasma cell dyscrasia

If the patient's diagnosis is confirmed to be myeloma and they do not proceed to trial registration, or a diagnosis of other plasma cell dyscrasia is confirmed (i.e., MGUS, SMM, POEMS, amyloidosis, solitary plasmacytoma), the bone marrow samples will either be destroyed or retained for future research as per the patient's wishes as documented on the Bone Marrow Sharing ICD. If the diagnosis is confirmed as not being myeloma or other plasma cell dyscrasia then the samples will be destroyed.

Where the patient does not proceed to trial registration following bone marrow registration, the research site should complete the non-trial registration eCRF to document:

- Ethnicity,
- Confirmed diagnosis, and
- *If diagnosed with myeloma*, reason for non-trial registration.

18.6. Two-stage trial consent process

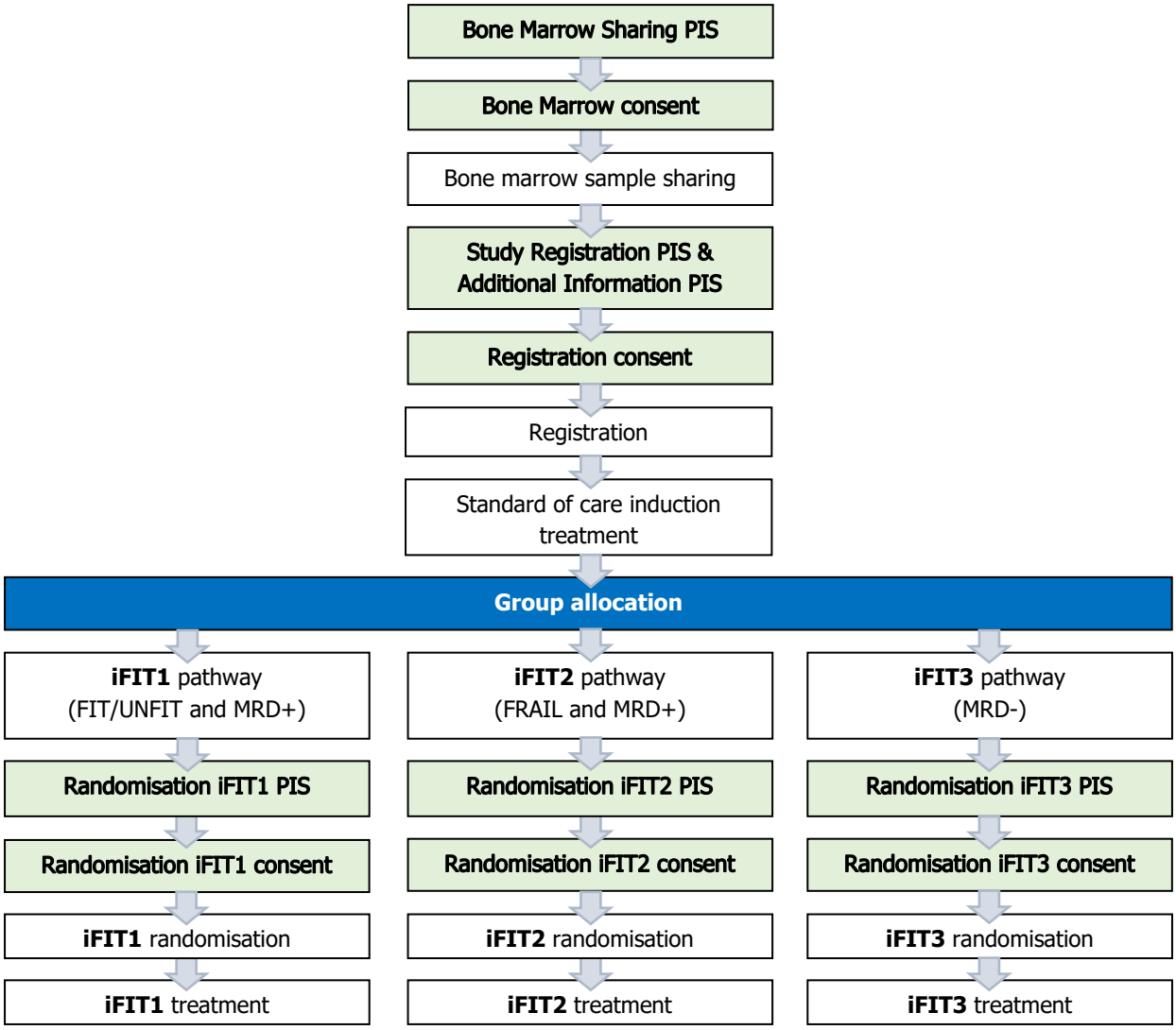
The informed consent process for receiving treatment on iFIT is carried out in two stages:

- Consent for registration, and
- Consent for entry into the **iFIT1**, **iFIT2,** or **iFIT3** randomisation pathways (separate PISICD for each).

The reason for the staged consent process is due to the complex nature of the trial and the multiple different further treatments a participant could receive based on their individual data at the end of the standard of care induction treatment. The patient/participant will only be given information relevant to them to prevent unnecessary additional burden. Prior to trial registration, all potential participants will be given the Study Registration PIS and Additional Information PIS (see Section 18.7.1). Once it is known which randomisation pathway the participant will be assigned to (expected to be around standard of care induction cycle 6 day 28), the participant will be given another PIS specific to the pathway they have been assigned to. This will include information on the further trial treatment they may receive (see **iFIT1** Section 30.3.1, **iFIT2** Section 37.3.1, **iFIT3** Section 44.3.1).

All PISs available for the trial (Bone Marrow Sharing, Study Registration, Randomisation **iFIT1**, Randomisation **iFIT2**, Randomisation **iFIT3**, Additional Information) will be available as paper copies or on the iFIT website (see Section 7) at any point throughout the trial.

Figure 2: iFIT trial consent process flowchart



18.7. Trial registration

18.7.1. Consent for trial registration

Once diagnosis is confirmed locally and the research site team consider the patient potentially eligible for the trial, the potential participant will be provided with a full verbal explanation of the trial and will be given a copy of the Study Registration PIS and Additional Information PIS to consider. The PISs include detailed information about the rationale, design and personal implications of the trial. The Study Registration PIS explains the standard of care induction treatment as well as what the patient should know about the trial overall. The Additional Information PIS is optional for the patient to read, if of interest, and does not contain information that is required for full informed consent. Following information provision, the patient will have as long as they need to consider participation and they will be given the opportunity to discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to take part in the trial. The right of a patient to refuse to take part in the trial without giving reasons must be respected.

Patients wishing to take part in the trial will be required to provide full informed consent using the Study Registration ICD.

The patient will be asked to self-report the following on the Study Registration ICD:

- Sex,
- Gender, and
- Ethnicity.

The following consent items will be optional:

- Consent for samples to be used in future research, and
- Consent to be contacted for qualitative interviews.

The medically QP taking consent should tick the box matching their clinical assessment of the patient's frailty on the consent form **before calculating the IMWG frailty score**, where asked to do so on the signature page.

18.7.2. Eligibility and baseline assessments prior to registration

Consenting patients will be formally assessed for eligibility in line with Section 17.1.

Initial assessment aiming to confirm eligibility and provide a baseline for the day-to-day clinical care of patients should be performed within 28 days prior to registration, unless otherwise stated below. If the start of DRd does not occur within 14 days post-trial registration, the tests will have to be repeated. The investigator must ensure that the imaging and bone marrow assessments are within 14 weeks of cycle 1 day 1. It is expected that all assessments will be performed as part of standard clinical care.

Unless otherwise specified, the date of the bone marrow sample and imaging, etc., is classed as day 1 within the trial and **NOT** day zero, unless otherwise specified.

Local Investigations: Eligibility* and baseline assessment
Please refer to the trial eCRFs to ensure you are familiar with all data collection items prior to completing assessments. The following assessments will be collected on eCRFs, unless specified otherwise:

- Myeloma diagnosis history*,
- Physical examination (including systolic and diastolic blood pressure, height, weight, vital signs (pulse, O_2 saturation, respiratory rate, temperature)),
- Medical history (including details of concomitant disease and medication, vaccination status and thorough review of previous malignancy history),
- Assessment of cardiac risk as part of standard care,
- Thyroid function monitoring as part of standard care,
- Full blood count (FBC), urea and electrolytes (U&Es), liver function test (LFTs), albumin, LDH, CRP, calcium, creatinine, urinary protein:creatinine ratio,
- Vitamin D and serum parathyroid hormone (if collected as part of local practice),
- β_2M,
- Calculated creatinine clearance (CrCl) (**CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospitals is not accurate in older patients**),
- Pregnancy test. Women of childbearing potential (WCBP) (see Appendix 48.10) must have a negative pregnancy test performed by a healthcare professional prior to starting treatment as per the pregnancy prevention plan for lenalidomide*,
- Hepatitis B (surface antigen and core antibody), Hepatitis C and HIV. PCR for active infection should be conducted if any of the antibody tests listed here are positive*,
- Serum paraprotein and immunofixation, SFLC, serum total (class-specific) immunoglobulins and urinary monoclonal protein detection (quantification where available)*,

- Bone marrow aspirate confirming myeloma diagnosis within 12 weeks prior to trial registration,
- Local cytogenetics report – send an anonymised copy with trial ID to CTRU after trial registration for central risk stratification (see Section 18.4), and
- Imaging of lytic and/or focal bone and extramedullary lesions as per local protocols/standard of care.
    - It is not necessary to repeat imaging if within **14 weeks** of registration since last performed, unless clinically indicated. As per NICE guidance, imaging at diagnosis can be whole body low-dose computed tomography scan (CT), magnetic resonance imaging scan (MRI), or position emission tomography scan with CT (PET-CT). MRI spine/pelvis alone is insufficient and should be supplemented by a whole body technique, e.g., whole body low dose CT. Note: imaging within 14 weeks prior to trial registration is mandatory.

18.7.3. Trial registration

Full informed consent for entry into the trial must be obtained prior to trial registration.

Once patients have given full informed consent using the Study Registration ICD and are confirmed eligible, they can then be registered. The patient will be allocated a trial number at the time of trial registration which will be used to identify the participant throughout the trial.

The following information will be required at trial registration:

- Research site name and site code,
- Bone marrow ID number (if patient was registered under bone marrow registration),
- Patient details, including initials, date of birth, sex and NHS/CHI number,
- Confirmation of eligibility,
- Confirmation of full informed consent for trial registration, and
- Confirmation of decision regarding optional consent items.

Care must be taken to ensure the correct "service" (iFIT trial), "event" (trial registration) and site code are selected/entered to ensure correct registration.

24-hour trial registration:

https://lictr.leeds.ac.uk/webrand/

Following trial registration, completed Study Registration consent documents must be sent via the CTRU Secure File Transfer Service or other CTRU-approved method (never standard e-mail).

Automated confirmation of trial registration will be emailed to the research site team.

The research site team should notify the participant's General Practitioner (GP) that they are taking part in the trial using the approved template letter provided by the CTRU. A copy of the letter should be filed in the ISF.

The local hospital will provide each participant with the standard of care daratumumab **safety card**, as per usual practice. The participant should carry this with them at all times and present to medical staff should they be admitted to hospital during their time on the trial.

18.7.4. Patients who did not consent for bone marrow samples at the time of routine diagnostic investigations

If the patient did not consent for bone marrow samples at the time of routine diagnostic investigations, a repeat bone marrow sample must be taken and sent to the central laboratories in line with Section 18.5.3.

The repeat bone marrow sample must only be performed following full informed consent for trial registration and trial registration.

18.8. Trial assessments

A tabulated summary of all local and central assessments is provided in Appendix 48.6.

Please refer to the trial eCRFs to ensure you are familiar with all data collection items prior to completing assessments. The assessments will be collected on eCRFs, unless specified otherwise.

18.8.1. Trial assessments prior to the start of DRd induction

The following assessments are to be carried out for all participants after trial registration and within 14 days prior to commencing standard of care induction treatment:

- Frailty assessments (see Section 18.10),
- QoL and healthcare resource use questionnaires (see Section 18.11), and
- Baseline central investigations:
    - HMDS:
        - Bone marrow aspirate (5mL) in EDTA for MRD *(if not already obtained and sent from the diagnostic bone marrow),*
    - RMH/ICR:
        - Bone marrow aspirate (5mL) in EDTA for translational work *(if not already obtained and sent from the diagnostic bone marrow),*
        - Peripheral blood (20mL) in EDTA for translational work, and
        - Clotted blood (10mL) for translational work.

Please note:

- Local bone marrow aspirate confirming myeloma diagnosis must be dated within 12 weeks prior to the date of main trial registration. Central bone marrow samples must be dated within 14 weeks prior to the start of treatment. If the bone marrow aspirate falls out of the specified timeline it will also need to be repeated.
- Please be aware that you do **NOT** need to await any confirmation of diagnosis from central samples to proceed with registration consent/trial registration. **ALL** assessments for diagnosis, eligibility and baseline data, etc., are based on local samples rather than results from central laboratories.

18.8.2. Trial assessments during DRd induction

The following assessments are to be carried out for all participants within the timeframe of day 1 (or ≤5 days prior), unless otherwise specified below, for each cycle of DRd induction:

- Physical examination (including systolic and diastolic blood pressure, height, and weight),
- Adverse events assessed by National Cancer Institute (NCI) CTCAE V5 grades,
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, creatinine, creatinine clearance, CRP, and immunoglobulin G (IgG). Creatinine clearance should be calculated using the Cockcroft-Gault formula, as the estimated GFR produced in most hospitals is not accurate in older patients.,
- Serum paraprotein and immunofixation, SFLC, and urinary monoclonal protein detection (quantification where available),
- An assessment of disease response according to the IMWG Uniform Response Criteria (see Appendix 48.2) is required at the end of each cycle of treatment. Samples for this assessment

must be taken at, or ≤5 days prior to, cycle 1 day 1 of the next cycle to provide a response. Please note where participant has non-secretory disease, adequate imaging and bone marrow sampling to monitor for response and PD must be performed,
- Pregnancy test. WCBP (see Appendix 48.10) must have a negative pregnancy test performed by a healthcare professional on day 1 (or ≤3 days prior) of each cycle of treatment (as per the pregnancy prevention plan for lenalidomide), and
- Pregnancy prevention counselling.

The following assessments are to be carried out for all participants in accordance with IMWG recommendations for response assessment and NICE guidance and if clinically indicated (standard of care):

- Cross-sectional imaging according to local practice. For monitoring accepted methods include whole body low dose CT, MRI, or PET-CT. MRI spine/pelvis alone is insufficient and should be supplemented by a whole body technique, e.g., whole body low dose CT. Additional imaging is not required by the trial protocol.

18.8.3. Trial assessments after 3 cycles of DRd induction

In addition to the trial assessments in Section 18.8.2, the following assessments are to be completed at cycle 3 day 28 (or ≤5 days) of DRd induction:

- Frailty assessments (see Section 18.10), and
- β_2M.

18.8.4. Trial assessments during/after 6 cycles of DRd induction

In addition to the trial assessments in Section 18.8.2, the following assessments are also to be completed between day 15 and day 21 of standard of care induction cycle 6:

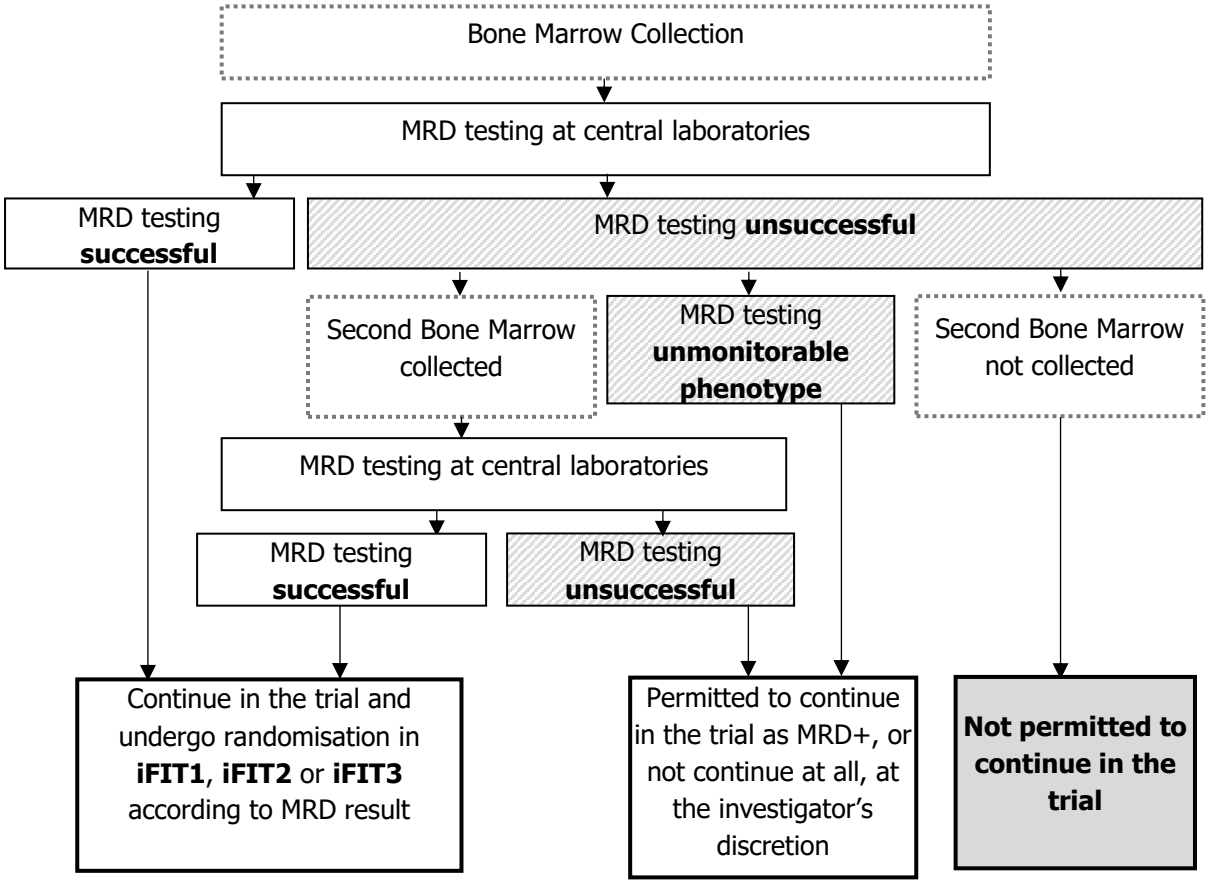
- Frailty assessments (see Section 18.10),
- β_2M,
- Infection prevention assessment, including prophylactic medications for infection given,
- Central investigations:
    - HMDS:
        - Bone marrow aspirate (5mL) in EDTA for MRD,
    - RMH/ICR:
        - Bone marrow aspirate (5mL) in EDTA for translational work (**first 400 participants only; we will tell research site teams when to stop sending this sample**),
        - Peripheral blood (20mL) in EDTA for translational work, and
        - Clotted blood (10mL) for translational work, and
- Response assessment:
    - Serum paraprotein and immunofixation, SFLC, serum total (class-specific) immunoglobulins and urinary monoclonal protein detection (quantification where available), and
    - Disease response assessment according to IMWG response criteria (see Appendix 48.2).

All participants* will have a bone marrow sample taken for an MRD test between day 15 and day 21 of standard of care induction cycle 6. If an MRD result cannot be obtained at the first attempt due to poor sample quality, the bone marrow should be repeated once (the second sample must be taken within 6

weeks after cycle 6 day 28 of standard of care induction). If the second attempt fails, it is permitted for the participant to continue within the trial classified as MRD+ or not continue at all, at the investigator's discretion. The participant cannot continue as MRD- without confirmation from HMDS. If a second attempt to obtain an MRD result is not made, the participant cannot continue on the trial.

*If the participant has an unmonitorable phenotype, as confirmed by CTRU, they are not required to have a bone marrow sample taken during cycle 6. It is permitted for the participant to continue as MRD+ or not continue at all at the investigator's discretion.

Figure 3: Bone marrow MRD testing process flowchart



The CTRU will feed back the MRD result via the MACRO database and email to the research site. This will be used to inform the participant's assignment to **iFIT1**, **iFIT2**, or **iFIT3**.

The following assessments are also to be carried out after 6 cycles of standard of care induction:

- QoL and healthcare resource use questionnaires (see Section 18.11).

18.9. MRD assessments

MRD assessment will be performed at the central laboratory (HMDS, Leeds Teaching Hospitals NHS Trust) with extensive previous experience of such analyses both reporting sub analysis of prior studies [15, 68] and in guiding trial therapy [69]. MRD negativity will be defined as absence of plasma cells with a neoplastic phenotype, using an assay with a minimum sensitivity of 1 in 100,000 leucocytes (i.e., 10^{-5}). MRD analysis will be performed by multi-parametric flow cytometry using a previously validated methodology [68]. In brief, whole bone marrow aspirate samples will be treated with ammonium

chloride to obtain leucocytes, which will be incubated with an antibody combination of at least 8-colours including CD138/CD38/CD45/CD19/CD56/CD27/CD81/CD117. Following incubation and washing, a minimum of 2,500,000 cells will be acquired and assessed. Patients will only be considered MRD negative if they are in at least a VGPR serologically and their bone marrow aspirate is MRD negative.

18.10. Frailty assessments

At the time of consent using the Study Registration ICD, the medically QP taking consent should indicate their clinical assessment of the patient's frailty, **before calculating the IMWG frailty score**.

Frailty assessments will be carried out for all participants until progression or withdrawal from trial treatment at the following timepoints during standard of care induction:

- Baseline,
- At cycle 3 day 28 (or ≤5 days) of standard of care induction treatment, and
- Between day 15 and day 21 of cycle 6 standard of care induction treatment.

The frailty assessments to be carried out during standard of care induction are as follows:

- IMWG frailty index (Charlson Comorbidity Score, ADL and IADL – see Appendix 48.3),
- ECOG and Karnofsky Performance Status (see Appendix 48.4),
- iFIT frailty assessments: 4 metre timed walk, clinician-led 3-word recall and clock drawing,
- G8 questionnaire, and
- Falls within the last 3 months.

See Section 22.1 regarding source data for these assessments.

18.11. Quality of life (QoL) and healthcare resource use questionnaires

In order to understand the QoL impact of treatments, participants will be asked to complete the following QoL questionnaires at the specified timepoints which have been selected due to their validation in myeloma:

- EQ-5D-5L,
- EORTC QLQ-C30,
- EORTC QLQ-MY20,
- EORTC QLQ-IL413,
- EORTC QLQ-IL414 (after 6 cycles of standard of care induction treatment and **iFIT1** participants only),
- Scale of Subjective Total Taste Acuity (STTA) (after 6 cycles of standard of care induction treatment and **iFIT1** participants only), and
- Healthcare resource use questionnaire.

The Myeloma Patient Outcome Scale (MyPOS) questionnaire was considered for collection, however, due to overlap with the EORTC-QLQ-MY20 it has not been included. Research sites may consider use of this locally.

Participants will be asked to complete the questionnaires at the following timepoints:

- Baseline,
- After 6 cycles of standard of care induction treatment, and
- At 3, 6, 12, 18, 24, and 30 months following **iFIT1**, **iFIT2** or **iFIT3** randomisation.

QoL questionnaires during standard of care induction treatment will be completed on paper by the participant. They should be given to the participant during clinic visits at the timepoints specified above

or posted by the research site to the participant's home address. Participants in **iFIT1**, **iFIT2** or **iFIT3** have the option to continue to complete questionnaires on paper in this way, or complete questionnaires online.

Participants completing paper questionnaires should be given an envelope to seal their questionnaires prior to return to the research site. This is to preserve the confidentiality of their answers. The research site should post the paper questionnaires (within the sealed envelope) to the CTRU. Should questionnaires be posted to the participant by the research site, an addressed envelope should be provided so that the questionnaires can be posted directly back to the iFIT team at the CTRU. The research site should not read, copy, or retain the questionnaires. Postage costs are the responsibility of the research site.

The questionnaires during standard of care induction treatment are due at certain cycles of treatment, when the participant should be visiting clinic for treatment. Post-randomisation the questionnaires are due based on time from randomisation. The research site should give the participant the questionnaires to complete when visiting clinic as close to each timepoint as possible. If a participant is not due in clinic when the questionnaire is due the research site should post to the participant's home address for completion.

Participants completing questionnaires online post-randomisation will be sent links to complete, reminders to complete and a 'thank you' for having completed by email and/or text from the CTRU. The questionnaires will be self-completed by the participant using a platform called Research Electronic Data Capture (REDCap). A maximum of 3 reminders by email and/or text will be sent for each timepoint. A thank you message will be sent by email and/or text post-completion for each timepoint. The research site should remind the participant that guidance for completing online questionnaires is provided in the Additional Information PIS. Should participants visit clinic around the time the questionnaires are due, the research site should ask participants if they have completed their questionnaires online, and if not, prompt them to complete.

Participants will continue to be asked to complete questionnaires at all timepoints specified regardless of whether previous questionnaires have been completed, unless they express a wish to withdraw consent for this part of the trial. If they express a wish to withdraw consent to be sent QoL questionnaires, they will be asked if they would be willing to complete the EORTC QLQ-IL6, which is the global health status (GHS)/QoL scale score of the EORTC QLQ-C30. If they say no to this, they will not be asked to complete any further questionnaires.

18.12. Imaging scans

Imaging scans [70] are to be carried out as per local standard practice at the following timepoints:

- Diagnosis,
- PD, and
- For disease monitoring, in accordance with IMWG recommendations for response assessment and NICE guidance and if clinically indicated (standard of care).

Imaging can be whole body low-dose CT, MRI or PET-CT. Anonymised copies of the imaging scan reports will be collected by the CTRU for central monitoring.

If the last imaging scan was performed more than 14 weeks prior to trial registration, the imaging scan must be repeated for research purposes. No other additional to standard of care imaging scans are mandated as part of the trial.

18.13. Qualitative assessments

This work is subject to further funding and ethical approval.

A sample (30) of consenting participants will be interviewed around the time of completion of frailty assessments after cycle 3 and cycle 6 of induction DRd therapy. The semi-structured interviews will explore the participant's experience of first-line treatment and the practical implications. Participant consent to future contact about the interviews will be obtained via the Study Registration ICD. This is recorded at trial registration via the CTRU automated 24-hour web-based system.

18.14. Treatment discontinuation prior to randomisation

Participants are only considered to be off trial if they have stopped receiving all trial IMPs. If they are still receiving at least one trial IMP, they are considered on-trial. Once assigned to an iFIT pathway this may mean they are not eligible to proceed into the pathway.

Participants that discontinue trial treatment during or at the end of standard of care induction, and do not proceed to randomisation, will not be followed up beyond the end of standard of care induction.

See Section 18.15 if the treatment discontinuation is due to PD. See Section 18.19 if the treatment discontinuation is due to participant withdrawal.

See Sections 30.5, 37.5, 44.5 for treatment discontinuation after randomisation for **iFIT1**, **iFIT2** and **iFIT3**, respectively.

18.15. Disease progression

Disease progression is defined as per IMWG criteria (see Appendix VII.48.248.2) and this defines the end of trial treatment.

Participants must attend clinic if PD occurs. The following investigations are performed at PD, in line with standard clinical care, and the applicable eCRF completed:

- Physical examination,
- ECOG and Karnofsky performance status,
- FBC, U&Es, LFTs, albumin, LDH, calcium, creatinine,
- CRP and β_2M,
- Serum paraprotein, SFLC, serum total (class specific) immunoglobulins and urinary monoclonal protein detection (quantification where available),
- Bone marrow aspirate and trephine,
- Imaging of lytic and/or focal bone and extramedullary lesions as per local protocols/standard of care. Note: In cases of new onset hypercalcaemia suggesting PD, imaging should be performed to confirm PD. Imaging can be whole body low-dose CT, MRI, or PET-CT,
- Central samples for translational work:
    - RMH/ICR:
        - Bone marrow aspirate (5mL) in EDTA,
        - Peripheral blood (20mL) in EDTA, and
        - Clotted blood (10mL), and
- Response and relapse assessment based on the IMWG response criteria (see Appendix 48.2), ensuring a second sample result is available that confirms disease progression.

Following PD participants' further management and subsequent treatment will be at the discretion of the treating clinician. Trial supplied medications (i.e., Dara-Tec and Dara-Tal in **iFIT1**) **must** cease when progression is confirmed.

18.16. Post-progression follow-up

Following PD all participants will be followed up annually until death, or until the end of the trial. Randomised participants will also continue to be asked to complete QoL/healthcare resource use questionnaires until 30 months post-randomisation.

18.17. End of active follow-up assessments

The clinical cut off for active follow up will be defined as the time at which the primary endpoint is met in each iFIT pathway, estimated to be 36 months after last patient first visit. After this time monitoring and data collection will be reduced to essential safety monitoring, and collection of PFS and OS events only in all pathways for a further 48 months.

18.18. Deaths

All deaths must be recorded on the Notification of Death eCRF within 24 hours of notification to the research site team.

All deaths should be assessed to determine whether they meet the criteria of an SAE, SAR or SUSAR. Definitions and reporting requirements for SAEs, SARs and SUSARs can be found in Section 20.

18.19. Withdrawals

Participants can withdraw from any of the following aspects of the trial at any time without giving a reason:

- Trial treatment
- Trial follow-up
- Collection of data from future routine healthcare appointments
- Blood and bone marrow sample collection/storage
- Collection of data from NHS England (or other central UK NHS bodies)
- QoL/healthcare resource use questionnaires,
- Use of samples in future research,
- Contact for interviews, and
- Use of anonymised data in further research projects.

Participant Withdrawal

The PI or delegate should ensure that the specific wishes of any participant who wishes to withdraw consent for further involvement in the trial, (be that from further treatment and/or follow-up data collection), are defined and clearly documented in the participant's medical notes and reported to CTRU using the Withdrawal Request eCRF. This is necessary so that the correct processes are followed by the CTRU and site following the withdrawal of consent.

Upon receipt of a Withdrawal Request eCRF, the CTRU will populate the ethically approved Participant Withdrawal Letter detailing the level of participant withdrawal and the withdrawal limitations as described above. The CTRU will send the populated letter to the research site team for them to send to the participant for confirmation. The participant will be instructed in the letter to contact the research site team if anything is incorrect.

If a participant withdraws from trial treatment prior to progression and not data collection according to the trial visit/follow-up schedule, study visits will continue every 2 months and the following central samples will be collected going forward where applicable:

After 6 cycles of DRd:

- HMDS: Bone marrow aspirate (5mL) in EDTA for MRD.

iFIT1/iFIT3:

- HMDS: Bone marrow aspirate (5mL) in EDTA for MRD:
    - 18 months from **iFIT1**/**iFIT3** randomisation, and
    - 30 months from **iFIT1**/**iFIT3** randomisation.

Progression: see Section 18.15 for details of the samples

If a participant withdraws consent for further trial treatment and/or further collection of data (from their standard of care visits/NHS England or other central UK bodies), their data and samples collected prior to withdrawal of consent will remain on file and will be included in the final study analysis. Data outstanding up to the point of withdrawal will be chased with site.

Participants who withdraw from further data collection according to the trial visit/follow-up schedule will no longer be able to be treated or actively monitored as per the trial visit/follow-up schedule.

It should be made clear to any participant specifically withdrawing consent for further data collection in a clinical trial of IMP (CTIMP) that **data pertaining to safety, for example SAEs and SUSARs, will continue to be collected for regulatory reporting purposes** and will be included in any safety analysis. In addition, it is suggested that the participant is made aware of the fact that if any significant new information becomes available regarding the treatment they have received in the trial it may be necessary to contact them in the future. These points are included within the ethically approved Participant Withdrawal Letter.

Where the participant withdraws their consent for completion of QoL/healthcare resource use questionnaires, questionnaires completed prior to withdrawal of consent will be included in the analysis.

Where the participant withdraws consent for their samples to be used in future research, this will be communicated to the laboratories and any samples which could be used for further analysis will be destroyed at the end of the trial. Some material from samples already processed may still need to be retained by the central laboratories for quality control purposes.

Clinician Withdrawal

If it is the decision of the attending clinician to withdraw the participant from further treatment then this should also be documented on the Withdrawal Request eCRF. It should be made clear to the participant that the trial visit and data collection schedule will continue as per protocol, unless the participant explicitly withdraws their consent for this.

18.20. Loss to follow-up

If a participant becomes uncontactable by the research site team prior to withdrawing from further data collection, they should be recorded as lost to follow-up on the applicable eCRF. Data up to the point the participant was lost to follow-up will continue to be chased. If available their data will still be obtained from NHS England or other central UK bodies.

18.21. Participant transfer

If a participant is being transferred to a different research site, the Participant Transfer eCRF should be completed.

18.21.1. Transfer to another research site that is participating in iFIT

Copies of any paper CRFs, ICDs and any other relevant correspondence is sent to the new hospital, with originals kept at the original research site. Data from before the date of transfer is queried with the original research site, and data after the transfer date is queried with the new research site. Both research sites must ensure that the participant transfer is recorded on the participant log in the ISF and Pharmacy Site File (PSF).

18.21.2. Transfer to another site that is NOT participating in iFIT

All trial treatment will cease. Any further treatment for MM received by the participant will be off-trial. The Withdrawal Request eCRF should be completed to record the completion of trial treatment/active monitoring.

If the participant agrees to be followed up at the new site, it is the responsibility of the original research site to gather follow-up data from the new site in order to the complete the eCRFs. The original research site will keep all trial documentation and ensure that the participant transfer is recorded on the participant log in the ISF and PSF.

If the participant does not want to be followed up at the new site, the original research site must complete the Withdrawal Request eCRF.

18.22. Protocol violations

Prospective, planned violations or waivers to the protocol are not permitted.

A protocol violation can be defined as: any accidental or unintentional change to, or non-compliance with the protocol that increases risk or decreases benefit, or has a significant effect on the participant's rights, safety, or welfare, or on the integrity of the data.

Examples of a violation include, but are not restricted to:

- Failure to obtain valid informed consent prior to performing any other trial investigation or procedure,
- Breaches of eligibility criteria,
- Drug administration errors relating to the IMP (e.g., overdose, underdose, not performing specified suitability for treatment tests, not modifying dose in line with required modifications), or
- Non-adherence to the protocol in relation to prohibited concomitant therapy whilst receiving trial treatment.

Protocol violations should be reported immediately to the CTRU using the Protocol Violations eCRF.

Protocol violations will be monitored and escalated to the TMG for review of medical significance. Medically significant protocol violations will be considered as to whether they meet the criteria for Serious Breaches of GCP (Section 24.4).

The following events do not need to be reported as a protocol violation as long as the local investigator deems it not medically significant, and the event does not result in an SAE/SUSAR:

- A rescheduled study visit,
- Participant refusal to complete scheduled research activities,
- Limited dosing errors by either participant or site, i.e., 1 or 2 missed doses of lenalidomide and/or dexamethasone within 1 or 2 cycles, that did not result in an SAE and that were deemed not medically significant by site. (Note: Where 3 or more doses are missed in one cycle, or one

or more doses are missed in 3 or more cycles for the same participant, the event must be reported as a protocol violation), or
- Treatment cycles that are 1 or 2 days short.

If the protocol violation is also associated with an event which meets the criteria of an SAE or SUSAR this should also be reported in accordance with Sections 20.4.3 and 20.4.1 of the protocol.

Protocol violations that repeatedly occur could constitute a serious breach (see Section 24.4).

18.23. Loss of capacity following informed consent

Where valid informed consent is obtained from the participant and the participant subsequently becomes unable to provide ongoing informed consent by virtue of physical or mental incapacity, the consent previously given when capable remains legally valid.

Participants who lose capacity after informed consent has been obtained will continue with protocol treatment and assessments in consultation with the PI and participant's carer/family with the participant's best interests foremost in the decision-making process. Ongoing collection of safety and follow-up data will continue via the clinical care team for inclusion in the trial analysis in order to preserve the integrity of the trial's intention-to-treat (ITT) analysis and fulfil regulatory requirements (particularly for pharmacovigilance purposes).

18.24. Collection and use of full participant name

Full participant name will be present on ICDs, which will be sent to the CTRU via Secure File Transfer. This information will be stored securely at the CTRU separate to all other iFIT trial data.

Full participant name will be requested with samples sent to HMDS central laboratory, along with NHS/CHI number, to ensure accurate identification for routinely returning results to research sites electronically and by post. Samples sent to RMH/ICR must **not** include participant name. Samples sent to RMH/ICR will include NHS/CHI number to ensure robust tracking and identification processes.

18.25. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Bone marrow and blood samples taken according to the trial schedule to be sent to central laboratories for the purposes of trial protocol endpoints are covered within the core consent given by the participant.

In line with the participant's consent wishes as detailed on the Bone Marrow ICD and/or the Registration ICD, samples may be stored for use in future myeloma research, and this may include giving access to samples to other research groups in the UK or abroad. Any future research will require ethical approval. Data protection regulations will be observed, and strict confidentiality maintained, and the participant will not be identified in the results of any future studies.

18.26. Storage and analysis of clinical samples

It is the responsibility of the research site to ensure that samples are appropriately labelled in accordance with the trial procedures to conform to the 2018 Data Protection Act and General Data Protection Regulation (GDPR). Biological samples collected from participants as part of this study will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act.

18.27. End of trial

The end of the trial is defined as the date of the collection of the last participant's last data item. Participants will be followed up until death or until the final analysis, whichever is sooner, as described in Sections 32, 39, and 46 for **iFIT1**, **iFIT2,** and **iFIT3**, respectively.

19. TRIAL TREATMENTS

Please refer to the iFIT Pharmacy and IMP Management Study Site Operating Procedure (SSOP) for full details of the trial IMP management requirements including IMP ordering, destruction, accountability and disposal records. The below are classed as IMPs during standard of care induction and if randomised to continue DRd/DR post-randomisation in **iFIT1**, **iFIT2**, or **iFIT3**.

For other IMPs in the randomisation pathways (daratumumab with teclistamab (Dara-Tec) and daratumumab with talquetamab (Dara-Tal)) in **iFIT1**, please refer to the individual pathway section for **iFIT1** (see Section 31).

19.1. Non-medical prescribing

Non-medical prescribing is permitted where non-medical staff are:

- Qualified independent prescribers,
- GCP trained,
- Delegated prescribing responsibilities by the PI, and this is recorded on the APL, and
- Permitted to prescribe within clinical trials according to local practice.

Non-medical prescribing is permitted for all trial IMPs and all trial stages.

Delegated prescribing responsibilities includes checking and approving pre-treatment blood results, reviewing new medications to ensure these are not prohibited or contraindicated and making dose adjustments in line with the protocol.

Medical review is required if this is local practice for these IMPs.

19.2. Name and description of daratumumab, lenalidomide and dexamethasone

19.2.1. Daratumumab

Daratumumab is given as an injection under the skin. Any brand/manufacturer of the IMP with a marketing authorisation (MA) in the UK can be used.

19.2.2. Lenalidomide

Lenalidomide is given orally as hard capsules. Any brand/manufacturer of the IMP with a MA in the UK can be used.

19.2.3. Dexamethasone

The form of dexamethasone used for DRd induction is at the discretion of each site, in accordance with local standard of care. Any brand/manufacturer of the IMP with a MA in the UK can be used. Soluble tablets, dexamethasone in solution form or IV dexamethasone may be used at the same dosage if participants experience difficulty with oral tablets.

19.3. Regulatory status of daratumumab, lenalidomide and dexamethasone

Daratumumab, lenalidomide and dexamethasone each have a MA in the UK.

19.4. Product characteristics

The Summary of Product Characteristics (SmPC) will be used for daratumumab, lenalidomide and dexamethasone.

CTRU will supply research sites with the SmPCs for the purposes of pharmacovigilance reporting (for determining causality of an event). This is not necessarily the most recent available version online.

19.5. Drug storage and supply of daratumumab, lenalidomide and dexamethasone

Storage of daratumumab, lenalidomide and dexamethasone IMPs is in line with the manufacturer's recommendations. For further details refer to the SmPC for each IMP. For DRd induction, DRd and DR post-randomisation, generic ("off the shelf") commercial supplies are to be used.

For "off the shelf" daratumumab, lenalidomide and dexamethasone stock used, the batch number and expiry date will be recorded on the trial-specific dispensing logs found within the PSF.

19.6. Preparation and labelling of Daratumumab, lenalidomide and dexamethasone

Local pharmacy will be responsible for labelling "off the shelf" daratumumab (as part of DRd/DR), lenalidomide and dexamethasone in accordance with the requirements of the Medicines for Human Use (MA, etc.) Regulations 1994. Local pharmacy will be responsible for producing these labels.

19.7. Routine tests before each DRd cycle

During the first 6 cycles of treatment DRd is planned to proceed according to standard of care and so routine tests are at the discretion of the treating clinician, in line with the SmPC. Please be aware that following entry into the iFIT pathways routine tests will be required to be closely aligned to the SmPC and so we recommend following the approach here from the start.

At day 1 (or ≤5 days prior to each DRd treatment cycle (standard of care induction and **iFIT1**, **iFIT2**, or **iFIT3** DRd/DR treatment, including cycle 1 day 1)) prior to treatment being given, participants will be assessed for their suitability for treatment. Following a break in treatment, assessment of suitability must still be carried out at day 1 (or ≤5 days prior to treatment re-commencing). Please see Section 18.8 for details of assessments to be performed.

For a new cycle of treatment to begin, the participant must meet the following criteria within the assessments performed as part of standard clinical care (day 1 or ≤5 days prior):

Haematological:

- ANC must be ≥ 1.0 x 10^9/L. Unless the participant has a known/suspected diagnosis of proven or presumed diagnosis of Duffy null phenotype neutropenia in which case an ANC ≥ 0.75 x 10^9/L is allowed. Granulocyte-colony stimulating factor (GCSF) support is allowed,
- For induction assessments performed, platelet count must be ≥ 50 x 10^9/L, or, in the case of heavy bone marrow infiltration (≥50%) which in the opinion of the investigator is the cause of the thrombocytopenia and provided appropriate supportive measures and participants' monitoring are

in place, platelet count between ≥ 30 < 50 x 10^9/L is permitted. Platelet transfusions are not allowed ≤ 3 days prior to study drug dosing for any dosing day, and
- Haemoglobin ≥ 80 g/L. The use of red blood cell transfusions is permitted.

Biochemical:
- Total bilirubin ≤ 3 x upper limit of normal (ULN), except in participants with congenital bilirubinaemia (Gilbert's Syndrome) in which case **direct** bilirubin ≤3 x ULN, and
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3 × ULN.

Non-haematologic toxicity related to study drugs (except for alopecia) must have resolved to ≤ grade 1 or to the participant's baseline condition, or to a severity level considered stable and tolerable by the investigator/participant, and in the opinion of the investigator safe to resume treatment.

If the participant fails to meet the above-cited criteria for initiation of the next cycle of treatment (including cycle 1 day 1 of DRd induction and cycle 1 day 1 of **iFIT1**, **iFIT2**, or **iFIT3** DRd/DR), dosing should be delayed for 1 week. At the end of that time, the participant should be re-evaluated to determine whether the criteria have been met. If the participant continues to fail to meet the above-cited criteria, the treatment should be delayed and continue to be re-evaluated. The maximum delay caused by failure to meet the above criteria before treatment should be discontinued will be 3 weeks unless discussed and agreed with the CIs. The maximum time before being considered off-trial will be 6 weeks unless discussed and agreed with the CIs.

Where treatment has been delayed for 3 weeks or more (regardless of the reason and not including between date of randomisation and cycle 1 day 1), then treatment cannot be (re)commenced without approval of the CIs (via the CTRU). If the delay is less than 3 weeks, then it is up to the treating clinician to determine. This also applies to delays mid-way through a cycle.

See Section 19.9 for information on dose modifications and delays.

Cardiac risk should be assessed and appropriately managed and monitored throughout treatment.

Thyroid function should be monitored regularly as per local standard of care.

19.8. Dosage schedules for daratumumab, lenalidomide, and dexamethasone

6 cycles of DRd will be given during standard of care induction. Participants may be randomised to continue DRd post-randomisation until PD, continue DR until PD, or continue DR for a further 18 cycles only in **iFIT1**, **iFIT2**, or **iFIT3**.

Each cycle is 28 days.

Table 2: Dosage schedules for daratumumab, lenalidomide, and dexamethasone

Drug	Route	Dose	Days
Daratumumab	SC	1800mg No adjustment recommended for frailty, in the event of renal or liver impairment, or for extremes of weight.	**Standard of care induction** Cycle 1 and 2: 1, 8, 15 and 22 Cycle 3-6: 1 and 15 **(Post-randomisation** Day 1 for all cycles)

Lenalidomide*	PO	Adjustments for renal function (these supersede any adjustments for frailty that might be standard at site): • CrCl ≥30-<50 – maximum dose 10mg daily escalating to 15mg after 2 cycle if tolerated. • CrCl <30, not requiring dialysis – maximum dose 7.5mg daily (or 15mg alt days) • CrCl <30, requiring dialysis – maximum dose 5mg daily to be administer after dialysis on dialysis days	1 – 21
Dexamethasone*	PO	Age ≤75 40mg Age ≥76 20mg Dosing should be based on age at cycle 1 day 1 and should not change based on a subsequent birthday.	1, 8, 15, 22

*Lenalidomide and dexamethasone dosing can follow frailty adjusted dosing schedules if this is the standard practice at site. In this event dose selections for lenalidomide and dexamethasone that comply with the dose reduction tables below should be followed.

If following dose modifications for frailty the dose can be adjusted if frailty status changes and can be escalated in the event of suboptimal response if well tolerated at current dose level. At all times dosing for renal dysfunction should take precedence.

Recommended pre-medications to be given 1 to 3 hours prior to the start of daratumumab for at least the first four doses:

- Paracetamol 1g, given orally,
- Chlorphenamine 4mg, given orally,
- The dexamethasone dose due for the day of treatment (this total dose can be split across the day of and day after daratumumab if preferred to add additional prophylaxis for delayed IRRs),
- Montelukast if respiratory co-morbidities per investigator discretion, and
- Addition pre-treatment medication such as H2-antagonists or antiemetics may be used per investigator discretion.

If dexamethasone in the DRd combination has been stopped for any reason (through pathway assignment or toxicity) then provided the participant has had at least four prior daratumumab doses with no IRR, then this can be omitted as a pre-medication. Similarly, the paracetamol and chlorphenamine can be stopped if there are no IRRs for at least four doses.

Additionally, for participants with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long-acting bronchodilators, and inhaled corticosteroids should be considered.

19.9. Dosage modifications for daratumumab, lenalidomide and dexamethasone

Participants should be monitored for toxicity.

During the 6 cycles of standard of care induction treatment, DRd is planned to proceed according to standard of care and so dose adjustments are at the discretion of the treating clinician or the participant themselves, in line with the SmPC. Following entry into **iFIT1**, **iFIT2**, or **iFIT3** pathways, dose

modifications will be required to be closely aligned to the SmPC and so we recommend following the approach here from the start.

Once a participant receives their day 1 treatment of a cycle this is classed as a cycle, and the cycle should last at least 28 days. If administrative reasons, e.g., bank holiday closures, necessitate a delay to the start of the subsequent cycle, then up to a week delay is permitted. This would also be acceptable for participants requesting breaks to go on holiday. Delays of longer than one week must be discussed with the CIs via the CTRU.

19.9.1. Daratumumab

No dose reductions of daratumumab are recommended. Dose delay may be required to allow recovery of toxicity (see below).

19.9.2. Lenalidomide

Dose reductions should be according to the following table as per the SmPC:

Table 3: Dose reductions for lenalidomide

Dose Level 0	25mg
Dose Level -1	20mg
Dose Level -2	15mg
Dose level -3	10mg
Dose level -4	5mg

19.9.3. Dexamethasone

Dose reductions should be according to the following table:

Table 4: Dose reductions for dexamethasone

Dose Level 0	40mg	20mg
Dose Level -1	20mg	10mg
Dose Level -2	10mg	6mg
Dose level -3	6mg	-

19.9.4. Dose modifications for toxicities

Dose modifications for haematological toxicities

A cycle of treatment should not normally be commenced if the Absolute Neutrophil Counts (ANC) < 1.0 x 10^9/L, and/or platelet count < 25 x 10^9/L. If the low counts are thought to be due to toxicity of the combination, then the actions below should be taken. If the low counts are thought to be due to myeloma bone marrow infiltration, the use of G-CSF and platelet support should be considered. If the cycle cannot commence due to haematological toxicity, then the whole treatment cycle should usually be deferred until recovery.

Table 5: Dose modifications for thrombocytopenia

When platelets	Daratumumab	Lenalidomide	Dexamethasone
< 25 x 19^9/L with bleeding	Hold	Hold	Hold

< 25 x 10^9/L no bleeding	Continue if considered safe to do so	Hold	Continue
Returns to ≥ 50 x 10^9/L	Continue	Decrease by one dose level when dosing resumed at next cycle	Continue

Table 6: Dose modifications for neutropenia

When neutrophils	Daratumumab	Lenalidomide	Dexamethasone
First fall to < 0.5 x 10^9/L	Hold	Hold	Continue
Returns to ≥ 1 x 10^9/L when neutropenia is the only observed toxicity	Resume	Resume lenalidomide at starting dose once daily, consider commencing GCSF	Continue
Returns to ≥ 1 x 10^9/L when neutropenia is not the only observed toxicity	Resume	Resume lenalidomide at next lower dose level once daily, consider commencing GCSF	Continue
For each subsequent drop below < 0.5 x 10^9/L	Hold	Hold	Continue
Returns to ≥ 1 x 10^9/L	Resume	Resume lenalidomide at next lower dose level once daily, commence GCSF if not already started	Continue

Dose modifications for other toxicities

For other grade 3 or 4 toxicities judged to be related to one of the agents in the combination, treatment should be stopped and only restarted when toxicity has resolved to ≤ grade 2 depending on the physician's discretion. For lenalidomide and dexamethasone this should be at the next lower dose level. Dose reductions for dexamethasone toxicity are at investigator discretion according to local protocols.

19.10. Known daratumumab, lenalidomide and dexamethasone reactions and interaction with other therapies

19.10.1. Daratumumab

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Infusion-related reactions (IRRs)

Daratumumab solution for SC injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 8% (95/1183) of patients experienced an IRR. Most IRRs occurred following the first injection and were grade 1-2. IRRs occurring with subsequent injections were seen in 1% of patients.

The median time to onset of IRRs following Daratumumab injection was 3.2 hours (range 0.15 to 83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension and blurred vision. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections.

Participants with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g., short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Patient observation for IRRs after administration of daratumumab should follow standard of care protocols.

Management of IRRs related to daratumumab

If an IRR develops during daratumumab SC administration, then the administration should be temporarily interrupted. Participants who experience AEs during daratumumab SC administration must be treated for their symptoms. Participants should be treated with paracetamol, antihistamine, or corticosteroids, as needed. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. If ocular symptoms (including choroidal effusion, acute myopia, and acute angle-closure glaucoma) occur, interrupt daratumumab and seek immediate ophthalmologic evaluation prior to restarting daratumumab. In the event of recurrent grade 3 IRR (or grade 2 event for laryngeal oedema or bronchospasm) or a single life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab SC should be discontinued.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh (Rhesus factor) blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

19.10.2. Lenalidomide

Venous and arterial thromboembolic events

In patients with MM, the combination of lenalidomide with dexamethasone is associated with an increased risk of VTE (predominantly deep vein thrombosis and pulmonary embolism) and an increased risk of arterial thromboembolism (predominantly myocardial infarction and cerebrovascular event).

Consequently, patients with known risk factors for thromboembolism – including prior thrombosis – should be closely monitored. Action should be taken to try to minimise all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidaemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events may also increase thrombotic risk in these patients. Therefore, erythropoietic agents, or other agents that may increase the risk of thrombosis, such as hormone replacement therapy, should be used with caution in MM patients receiving lenalidomide with dexamethasone.

Thromboprophylaxis is recommended in accordance with local guidelines. If the patient experiences any thromboembolic events, treatment must be discontinued and standard anticoagulation therapy started. Once the patient has been stabilised on the anticoagulation treatment and any complications of the thromboembolic event have been managed, the lenalidomide treatment may be restarted at the original dose dependent upon a benefit risk assessment. The patient should continue anticoagulation therapy during the course of lenalidomide treatment.

Oral contraceptives

No interaction study has been performed with oral contraceptives. Lenalidomide is not an enzyme inducer. In an in vitro study with human hepatocytes, lenalidomide, at various concentrations tested did not induce the cytochrome P450 enzyme (CYP)s CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4/5. Therefore, induction leading to reduced efficacy of medicinal products, including hormonal contraceptives, is not expected if lenalidomide is administered alone. However, dexamethasone is known to be a weak to moderate inducer of CYP3A4 and is likely to also affect other enzymes as well as transporters. It may not be excluded that the efficacy of oral contraceptives may be reduced during treatment. Effective measures to avoid pregnancy must be taken (see Section 19.13.1 and Appendix 48.10).

Warfarin

Co-administration of multiple 10mg doses of lenalidomide had no effect on the single dose pharmacokinetics of R- and S- warfarin. Co-administration of a single 25mg dose of warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use (concomitant treatment with dexamethasone). Dexamethasone is a weak to moderate enzyme inducer and its effect on warfarin is unknown. Close monitoring of warfarin concentration is advised during the treatment.

Digoxin

Concomitant administration with lenalidomide 10mg once daily increased the plasma exposure of digoxin (0.5mg, single dose) by 14% with a 90% confidence interval (0.52% to 28.2%). It is not known whether the effect will be different in the clinical use (higher lenalidomide doses and concomitant treatment with dexamethasone). Therefore, monitoring of the digoxin concentration is advised during lenalidomide treatment.

Statins

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone

Co-administration of single or multiple doses of dexamethasone (40mg once daily) has no clinically relevant effect on the multiple dose pharmacokinetics of lenalidomide (25mg once daily).

Interactions with P-glycoprotein (P-gp) inhibitors

In vitro, lenalidomide is a substrate of P-gp, but is not a P-gp inhibitor. Co-administration of multiple doses of the strong P-gp inhibitor quinidine (600mg, twice daily) or the moderate P-gp inhibitor/substrate temsirolimus (25mg) has no clinically relevant effect on the pharmacokinetics of lenalidomide (25mg). Co-administration of lenalidomide does not alter the pharmacokinetics of temsirolimus.

19.10.3. Dexamethasone

Rifampicin, rifabutin, carbamazepine, phenobartital, phenytoin, primidone, and aminoglutethimide enhance the metabolism of corticosteroids and its therapeutic effects may be reduced.

Dexamethasone is a moderate inducer of CYP3A4. Co-administration of dexamethasone with other drugs that are metabolized by CYP3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Ephedrine also accelerates the metabolism of dexamethasone.

The effects of anticholinesterases are antagonised by corticosteroids in myasthenia gravis.

The desired effects of hypoglycaemic agents (including insulin), anti-hypertensives and diuretics are antagonised by corticosteroids, and the hypokalaemic effects of acetazolamide, loop diuretics, thiazide diuretics and carbenoxolone are enhanced.

The efficacy of coumarin anticoagulants may be enhanced by concurrent corticosteroid therapy and close monitoring of the International Normalised Ratio (INR) or prothrombin time is required to avoid spontaneous bleeding.

Oral contraceptives (oestrogens and progestogens) increase plasma concentration of corticosteroids. The antiviral drug ritonavir also increases the plasma concentration of dexamethasone.

Dexamethasone reduces the plasma concentration of the antiviral drugs indinavir and saquinavir.

The renal clearance of salicylates is increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

Patients taking NSAIDs should be monitored since the incidence and/or severity of gastro-intestinal ulceration may increase.

Patients taking methotrexate and dexamethasone have an increased risk of haematological toxicity.

Antacids, especially those containing magnesium trisilicate have been reported to impair the gastrointestinal absorption of glucocorticoid steroids. Therefore, doses of one agent should be spaced as far as possible from the other.

19.11. Daratumumab, lenalidomide and dexamethasone

Complementary therapies including St John's Wort, and their interactions have not been fully studied for all IMPs and therefore should be avoided unless individually reviewed by local pharmacy and the treating physician.

19.12. Concomitant medication for daratumumab, lenalidomide and dexamethasone

Recommended infection prophylaxis (local policies can be followed if different to the below):

- Aciclovir 400mg twice daily,
- Co-trimoxazole 480mg twice daily on Mon/Wed/Fri (can be stopped if dexamethasone stopped),
- Fluconazole 50mg once daily (can be stopped if dexamethasone stopped), and
- Additional antibiotic prophylaxis, e.g., levofloxacin, if this is standard of care at site for the first 60 days.

Tumour lysis prophylaxis with allopurinol can be used at the investigator's discretion.

Thromboembolic prophylaxis is recommended according to local practice, e.g., apixaban 2.5mg twice daily.

19.12.1. Bone directed therapy during the trial:

There are no bone-specific interventions within the iFIT study, and bone anti-resorptive therapies will not be IMPs within the study. Instead, bone therapy-related questions will be investigated as an observational, cross-sectional objective for all participants in the iFIT study, in order to understand the current use of bone therapy for TNE patients in the UK. A recent national survey of UK practice (manuscript in preparation) indicates most patients would have planned bone therapy close to one of the following categories:

1) ZA monthly for 24 doses, then 3-monthly for a further 24 months, then stop,
2) ZA monthly for 24 doses, then stop,
3) ZA monthly for 12 doses, then a further decision at that point,
4) Pamidronate,
5) Denosumab,
6) No bone-directed therapy (e.g., if renal function precludes available options), or
7) Other (please specify).

The treating physician will therefore be asked at participant registration to specify which aligns most closely to their plan for bone-directed therapy for the participant.

Research sites will be asked to report intended, prescribed and received bone therapy on the relevant eCRF.

19.12.2. Prohibited con-medications for daratumumab, lenalidomide and dexamethasone:

1. Any treatment for myeloma, including participation in any other interventional study for myeloma that involves an IMP, is prohibited, except the following:
   a. Local radiotherapy to relieve bone pain, spinal cord compression or directed at an anatomically threatening lesion,
   b. Bisphosphonate or other bone-directed treatment, or
   c. Systemic corticosteroids for myeloma treatment as specified in the protocol (see Section 17) (steroid treatment delivered by any route for other co-morbid conditions is allowed when considered necessary by the treating physician).
2. Live vaccinations are contra-indicated.

19.13. Trial restrictions for daratumumab, lenalidomide and dexamethasone

Lenalidomide is structurally related to thalidomide, which is known to be teratogenic. If lenalidomide is taken during pregnancy, a teratogenic effect of lenalidomide in humans is expected. Prescribing of lenalidomide for the study must be in accordance with the trial-supplied SmPC and local pregnancy prevention protocols.

The effects of daratumumab during pregnancy are unknown. Female participants should avoid becoming pregnant and male participants should avoid impregnating a female partner. Daratumumab should be prescribed as outlined within this protocol and the trial-supplied SmPC.

19.13.1. Pregnancy testing and contraception during daratumumab, lenalidomide and dexamethasone

Patients taking DRd therapy who are WCBP (see Appendix 48.10) must use at least one method of effective contraception for at least 4 weeks before therapy, during therapy, and until at least 3 months after daratumumab and lenalidomide therapy. This should be continued in case of dose interruption OR commit to absolute and continuous abstinence confirmed on a monthly basis.

AND have a medical supervised negative pregnancy test performed by a healthcare professional:

- Prior to every cycle of treatment (during standard of care induction and as part of **iFIT1**, **iFIT2**, or **iFIT3** if taking lenalidomide) on day 1 (or ≤3 days prior) of each cycle,
- Every 4 weeks in the event of a dose delay, and
- At 4 weeks after the end of study treatment.

Male patients must use condoms during sexual intercourse throughout treatment duration, during dose interruption and for at least 7 days after cessation of treatment if their partner is pregnant or is a WCBP who is not using effective contraception and even if the male patient has undergone vasectomy. They should not donate semen or sperm during treatment including during dose interruptions and for at least 7 days following discontinuation of lenalidomide.

The approved methods of contraception are described in Appendix 48.10.

All patients should:

- Not donate blood during treatment and for at least 7 days after cessation of treatment with lenalidomide,
- Return any unused tablets to the hospital pharmacy, and
- Store medication safely at home to avoid accidental contact or ingestion by others.

All trial treatment is to be discontinued immediately if a pregnancy in a female participant or partner of a male participant occurs or is suspected, and the participant instructed to return any unused portion of the medication to the investigator.

19.14. Assessment of compliance with treatment during the trial

Participants will be asked to record treatment compliance with oral lenalidomide and dexamethasone using a Participant Diary Card that will be given to them prior to the start of each individual cycle of standard of care induction treatment/**iFIT1**/**iFIT2**/**iFIT3** treatment. Participants will also be asked to report any side-effects they experience for all trial treatment they receive. The participant will be asked to bring this card with them at every visit. All diary cards must be returned to the research site team to enable treatment compliance to be reviewed. Diary cards should not be sent to the CTRU.

In addition, participants should be instructed to return any unused tablets or capsules to the hospital pharmacy at each follow-up visit. Returned tablets or capsules will be destroyed per the iFIT Pharmacy and IMP Management SSOP for standard of care induction and applicable **iFIT1**/**iFIT2**/**iFIT3** treatment. Pharmacies do not need prior authorisation from the CTRU to destroy returned tablets or capsules.

Non-compliance with trial treatment should be reported to CTRU using the relevant eCRF. Repeated non-compliance with trial treatment may result in a discussion between the CIs and research site team, with a view to the participant being withdrawn from trial treatment if no longer able to meet protocol requirements.

19.14.1. Early trial treatment discontinuation

In line with standard clinical care, cessation or alteration of treatment regimens at any time will be at the discretion of treating clinicians or the participants themselves.

Participants who cease treatment for more than 6 weeks at any point in trial therapy including between the end of standard of care induction and commencing randomisation trial treatment will be considered off-trial and withdrawn from trial treatment unless discussed and agreed with the CIs.

If trial treatment is discontinued early (e.g., due to toxicity, clinician/participant choice, delay of >6 weeks unless discussed and agreed with the CIs) without the participant having reached a maximal response of at least PR, then the participant should be treated off-trial at the discretion of the investigator. Where maximal response of at least PR has been reached prior to discontinuation for any reason, in line with protocol further anti-myeloma treatment should not be given prior to PD.

For follow-up after early treatment discontinuation, please refer to Section 18.14 if prior to randomisation or if post-randomisation see **iFIT1** Section 30.5, **iFIT2** Section 37.5, and **iFIT3** Section 44.5.

20. PHARMACOVIGILANCE

20.1. Definitions

Table 7: Definitions of pharmacovigilance events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Events of special interest (AESI) and Special Situations – *relevant only to daratumumab with teclistamab and daratumumab with talquetamab combinations*	An adverse event of special interest (serious or non-serious) and a Special Situation are ones of scientific and medical concern specific to daratumumab (when in combination with teclistamab or talquetamab), teclistamab, and talquetamab (**iFIT1**), for which ongoing monitoring and rapid communication by the investigator to the sponsor could be appropriate. Such an adverse event or Special Situation might require further investigation in order to characterise and understand it. Depending on the nature of the adverse event or Special Situation, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant. The phrase "response to an IMP" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	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, or • jeopardises the subject or may require an intervention to prevent one of the above characteristics/consequences – herein referred to as "Other important medical events". *These characteristics/consequences have to be considered at the time of the event. For example, regarding a life-threatening event, this refers to an event in which the subject 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.* *Medical and scientific judgement must be exercised in deciding whether an event is "serious" in accordance with these criteria.*

Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the IMP in question set out in the reference safety information (Section 20.3)

20.2. Reference Safety Information (RSI)

The Reference Safety Information (RSI) is the identified section of the Investigator Brochure (IB) or Summary of Product Characteristics (SmPC) used for assessing the causality and expectedness of an adverse reaction.

The RSI in this trial is defined as:

- Section 4.8 of the trial-supplied SmPC for daratumumab,
- Section 4.8 of the trial-supplied SmPC for lenalidomide,
- Section 4.8 of the trial-supplied SmPC for dexamethasone,
- Section 4.8 of the trial-supplied SmPC for teclistamab, and
- Section 4.8 of the trial-supplied SmPC for talquetamab.

The version of the above SmPCs to be used for the purposes of pharmacovigilance reporting (in the case of this trial, for determining causality of an event) will be supplied to research sites by CTRU i.e., it is not necessarily the most recent available version online.

Please note that where the RSI (in Section 4.8 of the trial-supplied SmPC) does not explicitly state that expected SARs may be life-threatening/result in death, then such SARs which are life-threatening/result in death must be considered unexpected and reported as SUSARs.

20.3. Operational definitions – Serious Adverse Events (SAEs)

20.3.1. Events not classed as SAEs

The following events will not be recorded as SAEs within this trial:

- Hospitalisation for:
    - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition,
    - Treatment, which was elective and pre-planned, for a pre-existing condition not associated with any deterioration in condition,
    - General care, not associated with any deterioration in condition. This could be admission to hospital or other institution,
    - Treatment on an emergency, out-patient basis for an event not fulfilling any of the definitions for serious as given above and not resulting in hospital admission, or
    - Disease progression (disease progression must be reported on the Disease Progression eCRF – see Section 18.15), or
- Deaths attributable to myeloma beyond 60 days of the last dose of protocol treatment (deaths must be reported on the Death eCRF – see Section 18.18).

20.4. Recording and reporting of AEs, AESIs and Special Situations, SAEs, SARs and SUSARs

Due to the nature of MM and its treatment, participants are likely to experience several adverse events throughout the course of the disease.

Events will be reported on the eCRF using Medical Dictionary for Regulatory Activities (MedDRA) term(s) where possible and graded according to NCI-CTCAE V5 (see Appendix 48.5). A copy is provided in the ISF.

MedDRA coding of events will be performed centrally at CTRU.

Should an AE fulfil any of the SAE criteria described in Section 20.1, the SAE/SUSAR eCRF should also be completed.

Refer to the Pharmacovigilance SSOP for further reporting information.

20.4.1. AEs and ARs

All AEs, both related and unrelated to myeloma treatment, must be reported on the relevant eCRF from **trial randomisation** until 60 days after the last dose of protocol treatment or 60 days after the last cycle of active monitoring, as appropriate.

AEs may be spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures, and should be reviewed at each cycle of protocol treatment. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE, whether or not it is considered related to the IMP.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

20.4.2. AESIs and Special Situations (iFIT1)

AESIs and Special Situations must be collected and reported to CTRU on the applicable eCRF within one working day from the first dose of Dara-Tec or Dara-Tal treatment until 60 days after the last dose of treatment/60 days after the last cycle of active monitoring, as appropriate. AESIs and Special Situations in this study must be followed up until resolution or until there is no further improvement.

Teclistamab AESIs:

- Grade ≥ 2 cytokine release syndrome (CRS), including symptoms of CRS,
- Grade ≥ 2 immune effector cell associated neurotoxicity syndrome (ICANs), and
- Grade ≥ 2 non-ICANS teclistamab-related neurotoxicity

Talquetamab AESIs:

- Grade ≥ 2 CRS, including symptoms of CRS,
- Grade ≥ 2 ICANS, and
- Grade ≥ 2 non-ICANS talquetamab-related neurotoxicity

Special Situations:

- Exposure to daratumumab (when in combination with teclistamab or talquetamab in **iFIT1**), teclistamab and talquetamab during pregnancy (maternal and paternal)

- Suspected transmission of any infectious agent via administration of daratumumab, teclistamab or talquetamab

20.4.3. SAEs and SARs

All SAEs must be recorded on the SAE/SUSAR eCRF within 24 hours of the research staff becoming aware of the event, from **trial registration** until 60 days after the last dose of protocol treatment or 60 days after the last cycle of active monitoring, as appropriate.

All SARs must be recorded on the SAE/SUSAR eCRF within 24 hours of the research staff becoming aware of the event. SARs will be reported from the date of **trial registration** and for the duration of the trial.

Each SAE/SAR will be described by:

- symptoms/diagnosis,
- case description,
- event duration (start and end dates; times, if applicable),
- action taken in relation to IMPs,
- outcome,
- seriousness criteria, and
- causality, in the opinion of the investigator*.

*Assessment of causality must be made by a clinician. If a clinician is unavailable, initial reports without causality assessment must be submitted to CTRU without a clinician's assessment within 24 hours but must be followed up by medical assessment as soon as possible thereafter.

The CTRU will be responsible for determining the expectedness of each event in line with the RSI.

Should a clinician wish to provide comment on the expectedness of an event this must be made in line with the RSI (Section 20.2).

Please ensure that each SAE/SAR event is reported separately and not combined on one SAE/SUSAR eCRF.

Changes in SAE outcome, seriousness criteria, causality, or significant/medically relevant changes to the event (key data) must be reported within 24 hours of becoming aware. Other follow up information must be added to the SAE/SUSAR eCRF when the event has reached a final outcome, or when requested. Events will be followed up until the event has resolved or a final outcome has been reached. Investigators must report all SAEs to their host institution in line with their local arrangements.

20.4.1. SUSARs

All SARs assigned by the CTRU as being unexpected in line with the RSI will be classified as SUSARs and will be forwarded to the CIs (or delegate member of the TMG) for review and subject to expedited reporting to the relevant regulatory authorities.

Following the assessment of unexpectedness, CTRU will request the site research team complete any additional information on the SAE/SUSAR eCRF within 24 hours. The CTRU will inform the relevant regulatory authority, the Research Ethics Committee (REC), and the Sponsor of SUSARs within the required expedited reporting timescales. SUSARs will be sent to relevant pharmaceutical companies at the same time as submission to the relevant regulatory authority. SUSARs will be reported from the date of first study dose and for the duration of the trial.

Changes in SUSAR outcome, seriousness criteria, causality, or significant/medically relevant changes to the event (key data) must be reported within 24 hours of becoming aware. Other follow up information must be added to the SAE/SUSAR eCRF when the event has reached a final outcome, or when requested. Events will be followed up until the event has resolved or a final outcome has been reached. Investigators must report all SUSARs to their host institution in line with their local arrangements.

Refer to the Pharmacovigilance SSOP for SAE and SAR reporting.

20.5. Second Primary Malignancies (SPMs)

20.5.1. Recording and reporting SPMs

All new primary malignancies (termed "Second Primary Malignancies" – SPMs) or suspected malignancies occurring from trial registration for the duration of the trial must be recorded on the SPM eCRF **and** the SAE/SUSAR eCRF within 24 hours of the research site team becoming aware of the event.

All reported SPMs will be summarised and reviewed by an appointed member of the TMG. Additional information will be requested from the research site.

20.5.2. Continuation of treatment following SPM diagnosis

In the event of a new diagnosis of an invasive solid tumour malignancy or haematological malignancy the case should be discussed with the trial CIs and SPM clinical reviewer to consider whether the participant can safely continue on treatment within the trial.

Participants with non-invasive cancers as listed in the inclusion criteria for the study (see Section 29.1.2) can continue on trial at the discretion of the local investigator.

20.6. Pregnancies or suspected pregnancies

Pregnancy in participants on trial treatment must be prevented as effectively as possible. All guidance regarding contraception and pregnancy outlined in the lenalidomide, daratumumab, teclistamab and talquetamab SmPCs and Appendix 48.10 must be followed. Appropriate contraception must be used by female participants of child-bearing potential during treatment and for 3 months following cessation of protocol treatment (5 months if receiving Dara-Tec). Appropriate contraception must also be used by male participants with partners of child-bearing potential during treatment and for 7 days following cessation of lenalidomide treatment, or 3 months following cessation of teclistamab treatment.

All trial treatment must be stopped immediately if a pregnancy in a female participant occurs or is suspected. Participants must be instructed to return any unused portion of the medication to the investigator. Participants withdrawn from treatment will still attend for follow-up assessments unless unwilling to do so and CRFs will continue to be collected, see Section 18.19.

Female participants should be referred to an obstetrician/gynaecologist experienced in reproductive toxicity for further evaluation and counselling. If a pregnancy occurs in a male participant's partner, the partner should be advised to consult her GP or gynaecologist as soon as possible.

The local PI shall be responsible for any decision regarding the continued participation in the trial of participants who, after an initial positive pregnancy diagnosis, are confirmed as no longer being pregnant.

20.6.1. Recording and reporting pregnancies/suspected pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a female participant or a male participant's partner occurring from the time of full informed consent for registration until 3 months post cessation of trial treatment (5 months if receiving Dara-Tec) must be reported using the Pregnancy eCRF.

CTRU will report the pregnancy or suspected pregnancy to Johnson & Johnson Innovative Medicine as required and follow the pregnancy up to outcome.

Pregnant participants must be followed up until the end of their pregnancy and the CTRU must be notified of the outcome of the pregnancy (including false-positive pregnancy tests) within 24 hours of this information being known. If a pregnancy occurs in a male participant's partner, details of the pregnancy will still be collected where possible and the outcome of the pregnancy must be notified to CTRU.

If a female partner of a male participant taking IMP becomes pregnant, the male participant taking the IMP should notify the investigator. If a pregnancy related event is reported in a female partner of a male participant, the investigator should discuss the circumstances with the pregnant partner and contact CTRU-iFIT@leeds.ac.uk. **Only after contacting the CTRU should the investigator give the pregnant partner a copy of the Pregnant partner PISICD**. The Pregnant partner PISICD explains that the relevant information from them and their medical notes would be shared with Johnson & Johnson Innovative Medicine and the pregnancy related event be followed up until 28 days after birth.

The completed Pregnant partner ICD **must not be sent to the CTRU**. The right of a pregnant partner to deny their data being collected without giving reasons must be respected. The participant would be consulted about the pregnancy and the baby in all cases.

The outcome of any pregnancy which qualifies as a SAE (i.e., spontaneous or therapeutic abortion, foetal and neonatal death, or congenital abnormalities – including those detected in an aborted foetus), birth defects, or the death of an infant which occurs in connection with in utero exposure to the study drugs must be reported to the CTRU as a SAE in accordance with Section 20.4.3.

20.7. Responsibilities

Principal Investigator (PI):

- Checking for AEs and ARs when participants attend site for treatment, active monitoring, and follow-up, as appropriate,
- Ensuring that AEs and ARs are recorded, graded according to NCI-CTCAE V5 and reported to the CTRU in line with the requirements of the protocol,
- Using medical judgement in assigning seriousness and causality using the RSI approved for the trial,
- Ensuring that the site trial team are using the correct version of the safety reference document,
- Ensuring that all SAEs, SARs (including SUSARs), AESIs and Special Situations are recorded and reported to the CTRU within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs, SARs (including SUSARs), AESIs and Special Situations are chased with CTRU if a record of receipt is not received within 2 working days of initial reporting,
- Provide authorised sign off on the SAE/SUSAR eCRF, and

- In the case of pregnancy, ensuring that treatment is stopped immediately (in female participants), and the pregnancy is reported to the CTRU within 24 hours of becoming aware and followed up to outcome.

Chief Investigators (CIs)/delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk/benefit,
- Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the RSI) where it has not been possible to obtain local medical assessment,
- Using medical judgement in assigning whether an event/reaction was anticipated or expectedness in line with the RSI,
- Immediate review of all SUSARs,
- Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan (TMP),
- Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs, and
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

CTRU:

- Identifying at the beginning of the study the information in the SmPC or IB that will be used as the RSI for pharmacovigilance reporting,
- Central data collection and verification of AEs, ARs, SAEs, SARs, SUSARs, AESIs and Special Situations according to the trial protocol onto a MACRO database,
- Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk/benefit according to the TMP,
- Reporting safety information to the independent oversight committees identified for the trial DMEC and / or TSC) according to the TMP,
- Expedited reporting of SUSARs to the Competent Authority (Medicines and Healthcare products Healthcare Agency (MHRA) in the UK), main REC and Sponsor, within required timelines,
- Notifying Investigators of SUSARs that occur within the trial,
- Reporting events to collaborating pharmaceutical company in accordance with the trial contract,
- Checking for (annually) and notifying PIs of updates to the RSI for the trial,
- Notifying PIs of updates to the RSI for the trial,
- Communicating changes associated with a change in the risk/benefit ratio to research sites via a substantial amendment,
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CIs and ensuring timely submission to the MHRA and Main REC,
- Providing periodic safety reports to the DMEC,
- Notifying PIs at site(s), the Sponsor, main REC and MHRA of findings that could adversely affect the health of subjects, impact on the conduct of the trial or alter the authority's authorisation of the trial, and
- Monitoring research sites' compliance with safety reporting procedures and timelines.

Johnson & Johnson Innovative Medicine:

- Inform the CTRU/CIs of any new information which becomes available during the course of the study, which may affect the overall safety profile of the study drug.

Trial Steering Committee (TSC):

- In accordance with the TSC charter, periodically reviewing safety data and liaising with the DMEC regarding safety issues.

Data Monitoring and Ethics Committee (DMEC):

- In accordance with the DMEC charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis,
- Make recommendations that the trial continues to recruit participants or whether recruitment should be terminated either for everyone or for some treatment groups and/or some participant subgroups,
- Reviewing interim analysis results for **iFIT1** to assess early efficacy, and
- Reviewing interim analysis results for **iFIT3** to assess feasibility and early futility.

20.8. Notification of deaths

Deaths should be reported to the CTRU in line with Section 18.18.

Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This will be reported immediately.

20.9. Overdose

Overdoses should be reported as a protocol violation to CTRU in accordance with Section 18.22. An overdose is any medication that has been taken more frequently than expected or at a higher dose. It is expected that overdoses will be observed by the research site via participant completed diaries. The CTRU will discuss with the research site whether the patient should continue or be withdrawn from the trial following an overdose.

20.10. Reporting urgent safety measures

If any urgent safety measures are taken, the CIs or Sponsor shall notify the MHRA and the REC no later than 3 days from the date the measures were taken.

20.11. Development safety update report (DSUR)

The DSUR will be submitted by CTRU within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended.

21. STATISTICS AND DATA ANALYSIS

21.1. Sample size calculation

1226 patients will be registered into the trial to ensure at least 1165 participants remain and are assessed for MRD-negativity.

Sample size calculations for each randomisation pathway are in the individual pathway sections for **iFIT1** (Section 32.1), **iFIT2** (Section 39.1), and **iFIT3** (Section 46.1).

226 patients are required for **iFIT3**. Accounting for an approximate 3% drop-out, 233 patients are required to be MRD negative after 6 months of DRd induction. Using the assumption that 20% of patients will be MRD negative at this point (FiTNEss - unpublished data), 1165 are required to be assessed for MRD-negativity. Under the assumption that 95% of those who start DRd will be alive and progression-free at the end of induction [67], 1226 patients will be needed to enter the platform. Applying the assumption that 70% of MRD positive patients will be non-frail after 6 months of DRd (FiTNEss - unpublished data), the sample size of 1226 provides 652 patients for **iFIT1** and 279 for **iFIT2**. This provides a 10% drop-out for **iFIT1** and 42% for **iFIT2**.

The drop-out for **iFIT1** and **iFIT2** are larger than normal for a trial. However, they allow for variation in the estimates: these were based on FiTNEss, which used IRd rather than DRd, and so may result in more patients being MRD negative at 6 months. Finally, for **iFIT2** there is the possibility that it could be adapted in the future in response to emerging clinical evidence. All sample size assumptions will be monitored at meetings of the DMEC and recommended protocol changes implemented as required.

21.2. Planned recruitment rate

1226 patients will be recruited over a 48-month recruitment period across 80 UK research sites. Once all research sites are open the recruitment target is 30 participants per month.

21.3. Statistical analysis plan (SAP)

As the majority of objectives and endpoints are defined according to randomisation pathway, so are the SAPs. Refer to the individual pathway sections for **iFIT1** (Section 32.2), **iFIT2** (Section 39.2), and **iFIT3** (Section 46.2) for details. The analysis of the endpoints which consider treatment during standard of care induction and crosscut the iFIT randomisation pathways are considered here for completeness.

21.3.1. General considerations

Statistical analysis is the responsibility of the CTRU statisticians, with the exception of the analysis for cost-utility, which will be undertaken by the health economists at the University of Leeds. Full SAPs will be written before any analyses are undertaken.

For analyses carried out by CTRU, the analysis plan will be written in accordance with current CTRU SOPs and Johnson & Johnson Innovative Medicine templates and will be finalised and agreed by the following people: the Trial Statistician and Supervising Statistician, the Senior Trial Manager, the CTRU Scientific and Project Delivery Leads, the CIs, and a representative from Johnson & Johnson Innovative Medicine. Any changes to the finalised analysis plan, and reasons for changes, will be documented.

The analysis population used will depend on the pathway, with separate ITT populations, per-protocol (PP) populations, and safety populations defined for each; see Sections 32.2.1, 39.2.1, and 46.2.1 for **iFIT1**, **iFIT2**, and **iFIT3**, respectively. For analysis of the DRd induction period or across all iFIT pathways, the ITT population will include all registered participants. In each iFIT pathway, the ITT population will include participants according to their randomised treatment allocation. The ITT populations definitions apply regardless of participant eligibility, whether participants prematurely discontinued treatment, or did not comply with the treatment regimen. The PP population for each iFIT pathway will exclude participants who do not receive their randomised treatment or who are found to be ineligible following randomisation; no PP population is defined for the DRd induction period, as this is standard of care. The safety population for analysis of the DRd induction period, or across all iFIT

pathways, will consist of all participants who received at least one dose of daratumumab, lenalidomide or dexamethasone as part of induction therapy. In each iFIT pathway, the safety population will include all participants who received at least one dose of study treatment, according to the treatment received rather than randomised treatment allocation.

21.3.2. Frequency of analysis

Interim statistical summaries will be presented to the DMEC in strict confidence at approximately yearly intervals, as described in the DMEC charter.

Each pathway has a different number of formal interim analyses; see relevant sections for details. **iFIT1** has one interim analysis (Section 32.2.2), **iFIT2** has no interim analyses (Section 39.2.2), and **iFIT3** has two interim analyses (Section 46.2.2), for futility and feasibility, which will take place at the same timepoint.

No other formal interim analyses are planned before the participants have attained the primary endpoints, which will be triggered by the required number of events in each pathway. It is assumed that this will be 2 years following the end of recruitment for **iFIT1** and **iFIT2**, and 2.5 years following the end of recruitment for **iFIT3**. Analysis of other endpoints and secondary comparisons will be undertaken alongside these analyses, as appropriate.

Descriptive and/or exploratory analysis may be performed with the approval of the TMG, DMEC and TSC, where appropriate. These will be undertaken to develop abstracts for presentation at conferences throughout the duration of the trial to publicise the ongoing study and UK-MRA visibility. All abstracts containing trial data will be approved by the appropriate trial oversight committees before submission. If the analysis required exceeds that detailed within the final SAP, an analysis plan addendum summarising the additional analysis required will be written and added to the SAP as an appendix.

21.3.1. Summary of baseline data and flow of patients

The Consolidated Standards of Reporting Trials (CONSORT) [71] flow diagram will be used to summarise the course of participants through the study. Summary tables will show the number of participants in each analysis population. Summaries of protocol violations/deviations, including breaches of eligibility criteria and the reasons for non-registrations, withdrawals, and permanent discontinuation of treatment will also be presented. Additionally, summaries of follow-up time from registration will be presented overall.

The characteristics of those registered into the trial will be tabulated and appropriately summarised. Each summary will be presented overall and will include the information collected on the baseline eCRFs, including, but not limited to:

- Age (years) at registration,
- Sex,
- Ethnicity,
- Index of multiple deprivation (IMD),
- ECOG performance status at registration,
- Karnofsky performance status at registration,
- Paraprotein type,
- Light chain type,
- Immunoglobulin status at registration,
- Cytogenetic risk status,
- ISS at registration (see Appendix 48.8),

- R-ISS at registration (see Appendix 48.8),
- R2-ISS at registration (see Appendix 48.8),
- IMWG frailty category at registration (see Appendix 48.3), and
- UK-MRA MRP category at registration (see Appendix 48.9).

Categorical outcomes will be presented as numbers and percentages, using the total number of forms expected as the denominator; presentation of continuous outcomes will include means, standard deviations, medians, interquartile ranges, and ranges. Missing or unobtainable data will be included as missing in these summaries unless data are available from the 24-hour registration system. No statistical testing will be carried out when summarising these data.

21.3.2. Secondary endpoint analysis

The secondary endpoints which consider treatment during standard of care induction and crosscut the iFIT randomisation pathways are defined in Section 14.2.1.

To assess survival after progression, survival curves, plotting the time since progression against the proportion of participants alive, and the corresponding 95% confidence intervals will be estimated using the Kaplan-Meier approach. The median survival after progression times and 95% confidence intervals will be estimated from these plots. The percentages of those alive at yearly intervals following progression will also be estimated overall and by randomised treatment allocation along with 95% confidence intervals.

To assess ORR, the number and proportion of participants in each response category (sCR, CR, VGPR, etc.) will be summarised and exact 95% confidence intervals will be calculated.

To assess attainment of ≥VGPR and MRD negativity, the number and proportion of participants attaining these categories will be summarised and exact 95% confidence intervals will be calculated.

TTNT will be analysed using methods similar to those described for survival after progression, using the date of registration and the participant starting next line of treatment as the initial timepoint and event of interest, respectively.

Adverse events will be summarised using NCI-CTCAE V5.

Cumulative incidence function curves, plotting time since registration against cumulative incidence of SPMs, will be estimated along with 95% confidence intervals. Deaths not resulting from SPMs will be considered unrelated for this analysis, and participants affected will be censored at the date of death.

The incidence, type, and grades of infections along with any prophylactic treatment given during DRd induction therapy will be summarised descriptively.

QoL will be summarised descriptively using mean scores and 95% CIs, as well as median scores and the interquartile range, for each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role, and functioning domain and the EORTC QLQ-IL413 at each assessment timepoint. Similar descriptive summaries will be produced for QALYs, as scored by the EQ-5D-5L questionnaire. Multilevel modelling will be conducted to account for the longitudinal nature of the data, as well as the baseline QoL measurement. This, and procedures for missing data, will be detailed in the QoL SAP.

Objective measures of function will be assessed using the same methods as QoL measures, adjusting the timepoints and responses of interest as required.

21.3.3. Exploratory endpoint analysis

The categorical outcomes associated within the bone disease and therapy investigation will be summarised descriptively. This may be extended to subgroup analysis. Full details of the analysis will be included in the SAP.

21.4. Economic evaluation

It is not possible to conduct an economic evaluation of DRd induction, as DRd is now SoC in England and as there is no comparator in this stage of the trial. Instead, we will estimate costs and utility for DRd induction and compare these across subgroups. We will compare costs, QALYs and net health benefit across subgroups (notably, frailty groups) and with existing published estimates of value. We will report adjusted average costs and utility values for relevant groups (i.e., frailty groups and by overall response and MRD status).

Separate economic evaluations will be undertaken for the three randomisations. Each cost-utility analysis will follow the NICE reference case for health technology appraisals [72]. As such, outcomes will be measured in QALYs based on EQ-5D utilities and costs will be calculated from a health and personal social services perspective. Health related QoL will be captured using the EQ-5D (5 level) which will be completed at baseline and at follow up visits. The new UK tariff will likely be available at the time of analysis [73]. Bespoke questionnaires will be completed by participants at baseline and follow ups to gather data on community-based (e.g., visits with GPs, nurses, physiotherapists) and hospital-based (e.g., hospital attendances and A&E visits) healthcare resource utilisation. We will also capture secondary care resource use data from NHS Hospital Episodes Statistics. Unit costs will be taken from UK NHS Cost Collection, Personal Social Services Research Unit (PSSRU) and British National Formulary.

The three evaluations alongside the trial will use patient-level data accounting for trial stratification factors and adjusting as necessary for any imbalance between arms, treatment cross-over and correlation between costs and outcomes. Analysis outcomes will be presented as incremental cost-effectiveness ratios (ICERs; cost per QALY gain) and incremental net/health benefit. A cost-effectiveness threshold of £20,000-£30,000 per QALY gained will be assumed but we will determine whether these technologies are eligible for the NICE (1.2 or 1.7) severity modifier. Sampling uncertainty around the expected cost-effectiveness estimates will be determined.

We will adapt a lifetime horizon decision model, in development for the FiTNEss trial, to extrapolate costs and outcomes beyond the trial end; this will involve identification of suitable time-to-event curves for time-to-progression (TTP), time on treatment, post-progression survival and OS. We will consult the NICE Decision Support Unit guidance in this process. The model(s) will be developed using best practice [74] and the model structure, health states and parameter values will be derived from the trial outputs (FiTNEss and iFIT), published literature, and expert clinical opinion. We will seek to model subsequent treatments, either as separate tunnel states or via an expanded pathway modelling approach. We will also refer to previous technology appraisals (e.g., NICE [75]) to inform the modelling assumptions and parameters and to assess external validity. Model validation will follow published guidance [76], as will the reporting [77]. A formal evidence synthesis may be conducted should sufficient relevant studies be identified; this, along with previous trial data will be used to construct standard of care arm comparisons if required. The outputs will be ICERs, net benefit distributions and cost-effectiveness acceptability curves. Deterministic and probabilistic (using Monte Carlo simulations) sensitivity analyses will be conducted to explore the impact of single and combined parameter uncertainty on estimates of cost-effectiveness.

We will seek to apply the decision model at the interim analysis stage to estimate cost-effectiveness and undertake a value of information analysis [78] to estimate the value of trial continuation.

22. DATA MANAGEMENT – DATA COLLECTION, RECORDING AND HANDLING

22.1. Source data

Source data is defined as all information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of participants, source data will be accessible and maintained. Source data is kept as part of the participants' medical notes generated and maintained at site.

Source data should be clearly identified with awareness of the variation in practice at research sites.

Table 8 below is an example of the way in which source data can be identified.

Table 8: Examples of source data identification

Data	Source
Clinical Event Data	The original clinical annotation is the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g., phone calls), must be documented in the source documents.
Recruitment	The original record of the randomisation is the source. It is held on CTRU servers as part of the randomisation and data entry system.
Withdrawal	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source documents.
Participant Reported Outcomes	For methodological reasons (to avoid the risk of bias from participants knowing their care team will see their responses) it is CTRU policy for trial research sites not to have access to participant-reported outcome data. The source data is the paper form/REDCap form completed by the participant, and this is stored only at CTRU.
Frailty Assessment	A worksheet will be provided by the CTRU to record the frailty assessment and this can be filed or scanned into the patient notes to act as source data.

22.2. Source documents

Source documents are defined as "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after

verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial).

22.3. Completion and submission of trial data

ICDs and QoL and healthcare resource use questionnaires will be collected on paper. If a participant opts to complete questionnaires online post-randomisation, they will enter the data directly onto the REDCap database. All other data will be via Remote Data Entry (RDE) on eCRFs managed by the CTRU at the University of Leeds. If the trial electronic data capture (EDC) system is not accessible for any reason other than planned updates, paper versions of protocol violation, SAE, SUSAR, and SPM CRFs will be provided to allow reporting within 24 hours.

It is the responsibility of the PI to ensure the accuracy of all data entered in the eCRFs, either through providing their own authorisation (where required by CTRU) or through delegation to suitably trained and authorised data collection staff. The APL will identify all personnel with responsibilities for data collection.

Access to the live iFIT database will be provided by the CTRU following research site authorisation to open to recruitment. Access will be given only to those delegated to data collection and completion of eCRFs on the APL. Guidance on RDE and completing eCRFs will be provided.

Where additional information is required by CTRU, e.g., hospital reports, letters, etc., it is the responsibility of the research site team to redact all personal identifiable information prior to sending to the CTRU. Such records should only include trial number, initials and date of birth to identify the participant. The exception to this is the ICD, where the participant's name and signature must not be redacted.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried by CTRU Data Management. Staff delegated to complete paper forms and eCRFs will be trained to adhere to GCP requirements and trial-specific guidelines as appropriate.

Participating research sites will be expected to maintain a file of essential trial documentation in the ISF, which will be provided by the CTRU, and keep copies of all completed paper CRFs for the trial except for QoL and healthcare resource use questionnaires.

It is the responsibility of the site staff to ensure the ISF is properly maintained during the duration of the trial.

22.4. Paper case report form (CRF) completion

CTRU will provide an electronic copy of the relevant paper CRFs. The forms must be printed by staff at research sites and returned to CTRU as applicable. ICDs should be scanned and returned to CTRU via Secure File Transfer. Questionnaires must be returned via post, usually standard post. Back-up safety and Protocol Violations CRFs must be scanned and emailed to the trial inbox.

Participants completing paper questionnaires should be given an envelope to seal their questionnaires prior to return to the research site. This is to preserve the confidentiality of their answers. The research site should post the paper questionnaires (within the sealed envelope) to the CTRU. Should questionnaires be posted to the participant by the research site, an addressed envelope should be provided so that the questionnaires can be posted directly back to the iFIT team at the CTRU. The

research site should not read, copy, or retain the questionnaires. Postage costs are the responsibility of the research site.

22.5. Electronic Case Report Form (eCRF) completion

The delegated staff completing the eCRF should ensure the accuracy, completeness and timeliness of the data reported. This will be evidenced by data entry being completed in the EDC system's audit trail.

22.6. Data validation

Processes will be employed at CTRU to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in trial-specific data management documentation and include the processes of data entry, data queries and self-evident corrections on trial data, as applicable.

22.7. Access to data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent.

22.8. Data security

- The University of Leeds has policies in place, which are designed to protect the security, accuracy, integrity, and confidentiality of Personal Data.
- CTRU has arrangements in place for the secure storage and processing of the trial data which comply with UoL policies. The trial database system incorporates the following security counter measures:
    - Physical security measures: restricted access to the building, supervised onsite repairs and data backup on cloud,
    - Logical measures for access control and privilege management: including restricted accessibility, access-controlled servers, separate controls of non-identifiable data, and
    - Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.
- EDC System Design: The EDC System will comprise of a database and a data entry application with firewalls, restricted access, encryption, and role-based security controls.
- Operational Processes: Electronic data will be processed and stored within CTRU unless specifically noted.
- Data Protection Registration: The UoL's Data Protection Registration number is Z553814X
- NHS Digital Security and Protection Toolkit (DSPT) Organization code: ECC0010

22.9. Archiving

At the end of the trial, data will be securely archived in line with the Sponsor's procedures for a minimum of 25 years. Data held by the CTRU will be archived in the Leeds Sponsor archive facility and site data and documents will be archived at the participating centres. Following authorisation from the Sponsor, arrangements for confidential destruction will then be made.

23. MONITORING, AUDIT AND INSPECTION

Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it is received, confirmed as not available or the trial is at analysis. However missing data items will not be chased from participants (participants completing their questionnaires by post or online will be reminded – see Section 18.11). Data will be verified through both automated and manual checks and any queries returned to site for clarification and resolution. Any concerns with data completeness or quality will be fed back to site and may be raised with the relevant Local Clinical Research Network (LCRN) if appropriate. The CTRU/Sponsor will reserve the right to intermittently conduct SDV exercises on a sample of participants, which will be carried out by staff from the CTRU/Sponsor. Source data verification (SDV) will involve direct access to participant notes at the participating research sites and the ongoing central collection of copies of consent forms and other relevant investigation reports.

24. ETHICAL AND REGULATORY CONSIDERATIONS

24.1. REC review and reports

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th World Medical Association General Assembly, Edinburgh, Scotland, 1996. Full informed consent will be obtained from the patients prior to bone marrow registration, main trial registration and **iFIT1**, **iFIT2**, or **iFIT3** randomisation. The study will not commence recruiting participants until it has received all required approvals.

24.2. Patient and public involvement (PPI)

iFIT will incorporate a novel approach to PPI in collaboration with Myeloma UK, who will lead the SUAG. Patient voices are at the heart of Myeloma UK so using this model of collaboration offers many benefits, including access to a broad range of patients and carers, a well-supported environment for new PPI representatives and existing relationships built on trust. iFIT will test this model as a pilot, building in evaluations in collaboration between Myeloma UK and the CTRU, and sharing lessons learnt with other clinical researchers through dissemination at conferences.

The SUAG will meet regularly and feed into the ongoing development of the research, from set-up through to dissemination and beyond. The approach and design of Myeloma UK's PPI plan will follow the PPI Guidance set out by the NIHR and the Health Research Authority (HRA) and is built on methods they are also successfully employing in other funded research programmes.

Myeloma UK will aim to recruit people to be part of the SUAG from a wide range of demographics (i.e., range of ethnicities, socio-economic groups, genders, age, levels of education, years since diagnosis, etc.). SUAG members will be invited to attend regular SUAG meetings where they will act as independent advisors for the project. One of the SUAG members will be invited to attend the TMG alongside a representative from Myeloma UK.

As a minimum, it is expected that the SUAG will:

1. Review the proposed patient pathway and participant information sheets,
2. Review associated patient communications,
3. Identify barriers to recruitment requiring specific targeted approaches to resolve,
4. Be consulted on key decisions to provide a patient/carer perspective,
5. Review and provide insights on the research outcomes and analysis,
6. Engage in appropriate local and national engagement activities to promote the trial,

7. Help determine how the results should be disseminated to the patient and carer community, and
8. Review any journal articles and outputs, particularly any lay summaries that are required.

To evidence the impact of PPI during the trial, Myeloma UK will set up an activities tracker to record insights, input, and recommendations from the SUAG. SUAG members will be invited to complete a regular PPI Reflective Journal.

Data will be collected from and about consenting members of the SUAG and the iFIT central research team to determine the impact of PPI within iFIT. This will enrich our understanding of how PPI shaped this long-term research project and will act as an exemplar of how patients become immersed in research and PPI. This work will be approved separately.

We are committed to working collaboratively with all patient and carer representatives and will consider their needs, preferences and perspectives on how we can further develop their activities and any training or support they require to deliver these. These will be supported by Myeloma UK who have a tried and tested training manual for these activities.

Training and support for all PPI representatives will be offered by Myeloma UK in collaboration with The CTRU, who will provide supporting information prior to each TMG meeting and be present at SUAG meetings.

Patient representatives, independent of the SUAG, will also be invited to attend TSC and DMEC meetings via Myeloma UK or other avenues.

24.3. Regulatory compliance

The trial will be conducted in accordance with the principles of GCP in clinical trials, as applicable under UK regulations, the UK Policy Framework for Health and Social Care Research and through adherence to CTRU SOPs.

24.4. Notification of serious breaches to GCP and/or the protocol

CTRU and Sponsor have systems in place to ensure that potential serious breaches of GCP or the trial protocol are detected and reported. Investigators are required to promptly notify the CTRU of a potential serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and amendments) that they become aware of. A "serious breach" is a breach which is likely to effect to a significant degree

(a) the safety or physical or mental integrity of the subjects of the trial, or
(b) the scientific value of the trial.

In the event of doubt or for further information, the research site should contact the CTRU.

24.5. Data protection and patient confidentiality

The data controller for the trial is the University of Leeds. Participating research sites will be data processors for any trial data processing (while remaining data controllers of data processing required for patient care).

All data processing for the trial will be in accordance with the 2018 Data Protection Act and in line with the principles of the UK DPR. Personal data will be processed under a lawful basis of "task in the public interest" (GDPR Article 6, 1(e)) and special categories of personal data (in this case, data about health,

racial or ethnic origin and genetic data) will be processed for scientific research purposes (GDPR Article 9, 2(j)).

All potential trial participants are provided with detailed information about how their data will be processed before any personal data is processed for the trial. Any material changes to how data will be processed will be communicated to trial participants in a timely manner (prior to the changes, if reasonably possible).

Personal data will only be processed for specified, explicit and legitimate purposes, and will be adequate, relevant and limited to those purposes. Data will be stored and transferred securely for all processing. The trial will undergo an information governance risk assessment at the CTRU to ensure its proposed processing is compliant with data protection laws.

Confidentiality of participant data will be maintained at all times, with access to data granted only to those who need it for legitimate reasons (i.e., to conduct the trial, or to ensure the trial has been conducted lawfully). Participants will allow access to their confidential data through the informed consent process. In general, patients will be identified in the trial by their initials, date of birth and a trial-specific ID number. Research sites are responsible for maintaining this pseudonymisation on any data sent to the CTRU. Any exceptions (e.g., collecting unredacted consent forms at the CTRU for central monitoring of informed consent) will only be for legitimate reasons and will be explained fully to participants in advance of data processing. Where central monitoring of source documents, or copies of source documents, is required by the CTRU, the participant's name must be obliterated by site before sending. Any breach of confidentiality or of participants' personal data will be handled and reported (if required) in line with relevant laws.

Data will be made available for secondary research once the main trial objectives are complete. See Section 24.10 (Data sharing for secondary research purposes) below.

Trial data will be retained for a minimum of 25 years. When there is no longer a lawful basis for retaining the data, it will be securely destroyed.

24.6. Financial and other competing interests for the CIs and committee members for the overall trial management

Financial and other conflicts of interest will be collected for the CIs and members of the TMG, TSC and DMEC and stored at the CTRU.

24.7. Indemnity

The Sponsor has cover for liabilities/prospective liabilities arising from negligent harm. Clinical negligence indemnification rests with participating research sites.

24.8. Amendments

The CTRU will follow the REC/HRA/MHRA amendment processes.

It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC. If applicable, other specialist review bodies need to be notified about substantial amendments in case the amendment affects their opinion of the trial.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS Research and Development (R&D) office is based and communicated to the participating organisations (R&D office and local research site team) departments of participating research sites to assess whether the amendment affects the NHS permission for that site. Please note that non-

substantial amendments not applicable to any or some research sites will not require notification to some research sites by the CTRU.

The CTRU will be responsible for notifying the applicable authorities/review bodies/participating research sites of all substantial and non-substantial (where applicable) amendments.

Upon notification of an amendment to protocol or any other trial documents, the research site must supersede the document in their ISF/PSF and ensure that the current version is clearly filed for use.

Please see Section 6 for details on the most recent amendment to the protocol, and Appendix 48.11 for a full history of protocol amendments.

24.9. Post trial care

When the trial meets the end of trial definition, participants may continue to receive DRd treatment off-trial as this is a standard NHS treatment. Participants who are randomised to receive Dara-Tec or Dara-Tal in **iFIT1** will receive this treatment combination for a maximum of 18 cycles. Therefore, there is no required trial provision of IMPs post end of trial.

24.10. Access to the final trial dataset

Data sharing for secondary research

Individual participant data (with any relevant supporting material, e.g., data dictionary, protocol, SAP) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes at the end of the trial, i.e., usually when all primary and secondary endpoints have been met and all key analyses are complete.

Data will be shared according to a controlled access approach, based on the following principles:

- The value of the proposal will be considered in terms of the strategic priorities of the CTRU, CIs and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request,
- We encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets,
- The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team,
- Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. We will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. We will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants,
- Any data release must be in line with any contractual obligations to which the CTRU is subject,
- The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project,
- The research project must have clear objectives and use appropriate research methods, and
- The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate information technology security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.

Participants in this trial have not given explicit consent for their data to be shared for secondary research. However, they were provided with notification at bone marrow registration and/or main trial registration of our intention to make data available for further research. In addition, data will only be made available in such a way that data recipients cannot identify individuals by any reasonably likely means, and we will only share data for projects that are clearly in the public interest and compatible with the original purpose of the data processing.

Requests to access trial data should be made to CTRU-DataAccess@leeds.ac.uk in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

Samples will be made available for secondary research as per the participant's consent at trial entry. We will list available samples on HDR-UK Innovation Gateway and UK Clinical Research Collaboration UKCRC Tissue Directory to promote and allow access to the largest possible group of translational and discovery scientists and make these available with linked clinical data. It is currently anticipated that requests for sample access will be evaluated and managed by the TMG who will assess applications based on scientific quality and sample availability. However, there is national work ongoing via the UK-MRA-Myeloma UK Concept and Access Research Programme which is developing a national "virtual biobank" which allows real-time access to sample availability. This is being piloted in early phase trials in the first instance, but the intention is for it to be rolled out to phase III trials in the coming years. If the pilot is successful iFIT will be incorporated into this programme to improve discoverability. This programme also includes a tissue access group who will oversee all tissue access requests. Records of access requests and responses will be documented centrally at the CTRU. Access to samples from individual labs will not be granted without agreement of the TMG and Access Committee.

25. DISSEMINATION POLICY

25.1. Dissemination policy

The trial will be registered with an authorised registry, according to the International Committee of Medical Journal Editors (ICMJE) Guidelines, prior the start of recruitment.

The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. These state that authorship credit should be based only on substantial contribution to:

- Conception and design, or acquisition of data, or analysis and interpretation of data,
- Drafting the article or revising it critically for important intellectual content,
- Final approval of the version to be published, and
- That all these conditions must be met (www.icmje.org).

In light of this, the CIs and relevant senior CTRU staff will be named as authors in any publication. In addition, all collaborators will be listed as contributors for the main trial publication, giving details of roles in planning, conducting and reporting the trial.

To maintain the scientific integrity of the trial, data for secondary research will not be released prior to the first publication of the analysis of the primary endpoint, either for trial publication or oral presentation purposes, without the permission of the TSC and the CI. In addition, individual collaborators must not publish data concerning their participants which is directly relevant to the questions posed in the trial until the first publication of the analysis of the primary endpoint.

Publication of translational work (pre-specified or otherwise) that uses samples +/- outcome data from participants in the trial will be discussed with the CIs and agreed prior to submission. Authorship of such studies should include the CIs and other members of the TMG, if appropriate, based on contribution.

IV. iFIT1 RANDOMISATION PATHWAY

This section of the protocol is specific to the **iFIT1** pathway. This is applicable to **iFIT1** participants only and must be read in conjunction with the trial information applicable to all participants (Section III).

26. iFIT1 BACKGROUND AND RATIONALE

iFIT1 - incorporation of novel immunotherapeutic agents for patients with a suboptimal response to induction therapy and considered fit enough to receive immunotherapies

The novel bispecific antibodies teclistamab and talquetamab have demonstrated very high response rates and long duration of remission even in patients with very relapsed and/or refractory disease. Their use in newly diagnosed patients may have the benefit of being delivered in the context of immune-function less impacted by previous therapy and relapses of disease. The addition of TCE therapy to DRd could therefore be hypothesised to improve outcomes compared to DRd, but may be associated with increased toxicity such as infections. Our approach is to target the use of bispecific therapy to patients whose disease continue to have residual activity (does not achieve MRD negativity) after 6 cycles of DRd, and are classified as ”FIT” or ”UNFIT” by frailty assessment. The DRd induction phase should allow resolution of myeloma-driven frailty, enabling more patients to receive TCE therapy than excluding all those classified frail at diagnosis. In addition by removing some of the active myeloma burden patient immunological function may be more optimal. We have therefore taken this approach to balance potential toxicity against additive benefit, and also with a view to a more affordable strategic approach to the use of bispecific antibodies.

Teclistamab is a B-cell maturation antigen (BCMA) and CD3 targeting bispecific antibody immunotherapy. BCMA is highly expressed on the surface of myeloma cells and CD3 receptors on T cells meaning the bispecific antibody approximates and activates T cells leading to myeloma cell death. The phase I/II, multi-centre, open label study MajesTEC-1 [79] enrolled patients who had relapsed or refractory myeloma after at least three lines of therapy, including triple-class exposure to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody. Patients received SC teclistamab 1.5mg/kg weekly after a 2-step-up priming dose regimen (0.06mg/kg and 0.3mg/kg). 165 patients received teclistamab and at a median follow-up of 14.1 months the ORR was 63% and the MRD negative rate was 27%. This, along with other immunotherapeutic approaches, represents a step change in response rates for such a heavily pre-treated and refractory population leading to European Medicines Agency (EMA) approval for patients who have received at least 3 previous treatments for myeloma. Toxicity in MajesTEC-1 included infections in 76% of patients (grade 3 or 4 in 45%) and CRS in 72% (grade 3 or 4 in 0.6%). Moving teclistamab to first-line therapy has the potential to harness a more active immune microenvironment (after induction treatment with DRd) prior to exposure to multiple lines of therapy as well as treating a less aggressive myeloma clone. Additionally, the risk of infections may be reduced in less heavily pre-treated patients. iFIT offers an ideal trial in which to test this by giving it to the patients with the greatest need and who have had their fitness formally assessed as part of their treatment pathway.

Talquetamab is a GPRC5D and CD3 targeting bispecific antibody immunotherapy with a similar mechanism of action to teclistamab but targeting a different myeloma cell surface antigen. GPRC5D expression is enriched in myeloma cells and associated with genetically high-risk myeloma. In the phase

I, multicentre, open label study of talquetamab, MonumenTAL-1 [80], 232 patients received treatment. After dose escalation two dose expansion cohorts received SC talquetamab at either 0.4mg/kg weekly (n=30) or 0.8mg/kg every two weeks (n=44), after a 3-step-up priming dose regimen (0.01mg/kg, 0.06mg/kg and 0.4mg/kg). Patients receiving 0.4mg/kg weekly had an ORR of 70% (median follow-up 11.7 months) and those receiving 0.8mg/kg biweekly 64% (median follow-up 4.2 months). This data led to the European Medicines Agency (EMA) approval of talquetamab (0.8mg/kg bi-weekly) for patients who have received at least 3 previous treatments for myeloma. Toxicity in MonumenTAL-1 for those receiving 0.8mg/kg of talquetamab biweekly included CRS (in 80% of patients) as well as skin related events (in 70%) and dysgeusia (in 57%). The rate of infections appeared lower than with teclistamab. As with teclistamab, moving talquetamab to first-line therapy has the potential to lead to greater efficacy and the side effect profile differences warrant studying both therapies in this population.

Combining either teclistamab or talquetamab with daratumumab has potential synergy due to the immunomodulatory activity of daratumumab with evidence of upregulation of CD38+/CD8+ T cells and proinflammatory cytokines shown in preclinical studies [81]. The TRIMM-2 study (NCT04108195) had cohorts for both teclistamab plus daratumumab and talquetamab plus daratumumab. In the cohort combining teclistamab and daratumumab [82], patients with a median of 6 prior lines of therapy had an ORR of 77% with median PFS not yet reached. In the cohort combining talquetamab and daratumumab [83], patients with a median of 5 prior lines of therapy had an ORR of 78% with median PFS of 19.4 months. In both cohorts the toxicity was similar to teclistamab or talquetamab single agent despite evidence of enhanced activity.

iFIT1 will therefore address whether in patients fit enough to receive these agents (IMWG FIT/UNFIT) and with a suboptimal response to DRd, outcomes can be improved by switching to a daratumumab plus TCE combination, delivered for a limited duration of 18 months. Its design is also driven by patient priority setting, this pathway addresses James Lind Alliance priorities "How can we cure myeloma?" and "Are novel immunotherapies effective for the treatment of myeloma?".

26.1. Risk of infections

In studies of relapsed myeloma patients receiving bi-specific antibody there is a significant risk of infection with studies reporting a grade ≥3 infection incidence of 16% to 55% with BCMA targeting bi-specific antibodies, with a lower rate being observed with GPRC5D targeting treatments (16% to 22%) [84]. Real world data collated in over 200 patients, the majority of whom (87%) received BCMA targeting bi-specific antibodies, also reported infections in 62%, including 53% grade 3 and above with 8.4% dying consequent to their infective episode. [85] It is notable however, that the earlier landmark studies for the BCMA bi-specific antibodies [79], and indeed the reported real-world series [85], only included a minority of patients in receipt of IV immunoglobulin, which has been shown to reduce the incidence of infection by up to 90% [86]. Nonetheless, immunoglobulin replacement therapy does not entirely mitigate the infection risk, with a small retrospective study reporting hypogammaglobinaemia in all patients responding to a BCMA bi-specific antibody which occurred following the first cycle of treatment [86]. However, 92% of this cohort did receive immunoglobulin, yet grade 3 to 5 infections were still seen in 41%, with 84% of infections occurring during a period of disease remission [86]. A systematic review and meta-analysis of infections following bi-specific antibody treatment reported a significantly higher incidence of infection when bi-specific therapy is used in combination with another treatment with the incidence of all grade infections increasing from 52% (bi-specific only) to 71% (bi-specific in combination) with a trend towards an increased rate of grade ≥3 infections (44% vs. 52%, respectively) [87].

The nature of infections reported in patients receiving bi-specific antibody treatment includes both bacterial and viral infections, with bacterial infections being most common [85, 88]. It has been reported

that adapting the dose frequency in order to extend the interval between bi-specific treatments may reduce the incidence of infection [89]. In addition, supportive measures have been recommended to further reduce the likelihood of infection, which include commencing immunoglobulin replacement therapy, using GCSF for prolonged neutropenia, prophylactic aciclovir, and screening for cytomegalovirus , varicella zoster and herpes simplex viruses [90].

In order to monitor this risk and mitigation approaches closely we will collate the incidence of infective episodes during **iFIT1**. We will also collect participant experience of infections through a validated patient-reported outcome measure. Through exploratory analysis we will investigate the possible correlation of infective episodes reported during DRd treatment (see Section 13.7), and those subsequently reported following **iFIT1** randomisation to determine if there are disease- or patient-related factors that may enable prospective identification of patients at risk of infection, particularly those who are exposed to bi-specific antibody therapy.

27. iFIT1 OBJECTIVES AND ENDPOINTS

27.1. iFIT1 Primary objectives

To determine the impact on PFS when switching from DRd maintenance therapy to progression to either

a. Dara-Tec for 18 cycles, **OR**
b. Dara-Tal for 18 cycles.

in patients who are MRD positive and FIT/UNFIT by IMWG frailty assessment after six cycles of DRd induction therapy.

The alternative hypotheses are that the arms containing a TCE for 18 cycles will result in a difference in PFS at 24 months post-randomisation, compared to DRd maintenance therapy to progression. Superiority of the TCE containing arms is anticipated. The null hypotheses are that there is no difference in PFS at 24 months post-randomisation. No pairwise comparisons will be made between the TCE arms.

27.2. iFIT1 Secondary objectives

The secondary objectives are to assess the impact of switching from DRd maintenance therapy to progression to either

a. Dara-Tec for 18 cycles, **OR**
b. Dara-Tal for 18 cycles.

in patients who are MRD positive and FIT/UNFIT by IMWG frailty assessment after six cycles of DRd induction therapy, on the following endpoints:

1. Time to progression (TTP),
2. Time to second PFS event (PFS2),
3. Overall survival (OS),
4. Event-free survival (EFS),
5. Overall response rate (ORR),
6. Attainment of ≥VGPR,
7. Attainment of MRD negativity,
8. Maximum response,

9. Time to improved response,
10. Treatment compliance,
11. Toxicity and safety,
12. Incidence of secondary primary malignancies (SPMs),
13. Incidence, rate, and type of infections,
14. Quality of life (QoL), and
15. Cost-utility.

No pairwise comparisons will be made between the TCE arms.

27.3. iFIT1 Exploratory objectives

The exploratory objectives are to assess the impact of switching from DRd maintenance therapy to progression to either

a. Dara-Tec for 18 cycles, **OR**
b. Dara-Tal for 18 cycles.

in patients who are MRD positive and FIT/UNFIT by IMWG frailty assessment after six cycles of DRd induction therapy, on the following:

1. Infection interactions, and
2. Infection risk.

No pairwise comparisons will be made between the TCE arms.

27.4. iFIT1 Endpoints

Response to treatment, including progression, will be defined using the IMWG response criteria [91] (see Appendix 48.2) for all relevant endpoints.

27.4.1. iFIT1 Primary endpoint

Progression-free survival (PFS)
The time from **iFIT1** randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

27.4.2. iFIT1 Secondary endpoints

Time to progression (TTP)
The time from **iFIT1** randomisation to first documented evidence of PD. Participants who die without PD will be censored at their date of death. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Time to second PFS event (PFS2)
The time from **iFIT1** randomisation to the second documented evidence of PD or death from any cause. Participants alive and for whom a second PD has not been observed at the time of analysis will be censored at their last known date to be alive and second progression-free.

Overall survival (OS)
The time from **iFIT1** randomisation to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive.

Event-free survival (EFS)

The time from **iFIT1** randomisation to the first of the following events: grade 4 haematological AEs (anaemia, neutropenia, thrombocytopenia), grade 3 and 4 non-haematological AEs (including SPMs), discontinuation of trial treatment, progression or death. Events will be graded according to NCI-CTCAE V5. Participants event-free at the time of analysis will be censored at their last date known to be alive and event-free.

Overall response rate (ORR)
The categorical response to treatment at key timepoints: sCR, CR, VGPR, PR, MR, SD, or PD. This will be determined at the end of cycle 18 of **iFIT1** treatment, and cycle 30 of **iFIT1** treatment or cycle 12 of **iFIT1** active monitoring, as applicable.

Attainment of ≥VGPR
The binary response to treatment when ORR is dichotomised as ≥VGPR (sCR, CR, VGPR) versus <VGPR (PR, MR, SD, PD). This will be determined at the same key timepoints as ORR.

Attainment of MRD negativity
The binary MRD status, negative versus positive, as assessed by flow cytometry; MRD negativity is defined as at least a serological VGPR and MRD negative bone marrow aspirate at the 10^{-5} threshold. This will be determined at the same key timepoints as ORR.

Maximum response
The maximum response attained at any point after **iFIT1** randomisation.

Time to improved response
The time from **iFIT1** randomisation to first recorded improved response, where the baseline response is that recorded at the start of randomised treatment (**iFIT1** cycle 1, day 1). Participants whose disease progresses or who die before an improved response is recorded will be censored at the time of progression or death, respectively. Participants alive with no improved response recorded at the time of analysis will be censored at their last known date to be alive.

Treatment compliance
Compliance with **iFIT1** treatment will be assessed in multiple ways: a binary variable indicating whether all cycles of treatment were completed, the number of cycles completed, and the total dose of each trial medication received. The number and causes of dose omissions, dose delays, and dose reductions will also be reported, by trial IMP.

Toxicity and safety
All AEs, ARs, SAEs, SARs, SUSARs, AESIs, and Special Situations reported following **iFIT1** randomisation, as graded by NCI-CTCAE V5. Also included are the numbers of pregnancies in both trial participants and their partners where appropriate.

Incidence of secondary primary malignancies (SPMs)
The number and details of all other cancers, defined as SPMs, reported following **iFIT1** randomisation.

Incidence, rate, and type of infections
In the first instance, this is defined as the proportion of participants in the **iFIT1** pathway experiencing an infection of any type or grade, as graded by NCI-CTCAE V5. Rate of infection is the number of infections experienced divided by the total number of participant days in the **iFIT1** pathway. This will then be extended to consider grade 3, 4, and 5 infections only and then each type of infection (e.g., fungal, viral, bacterial) separately. This will be extended further to consider the results of viral PCR tests where appropriate.

Quality of life (QoL)

Health-related QoL, as scored using the following participant-reported questionnaires: EQ-5D-5L, EORTC QLQ-C30, and EORTC QLQ-MY20. Participant-reported infections will be assessed using the EORTC QLQ-IL413. Participant-reported oral health will be assessed using items from the EORTC QLQ-IL414 questionnaire and the STTA questionnaire. QoL questionnaires will be completed at 3, 6, 12, 18, 24, and 30 months post-**iFIT1** randomisation. End of DRd induction is defined as the baseline QoL in **iFIT1**.

Cost-utility

ICERs indicating cost per QALY will be the primary economic evaluation endpoint. Costs will include therapy and healthcare resource use costs. QALYs will be estimated using survival, adjusted for quality according to the EQ-5D-5L. Probability of cost-effectiveness and net health benefit estimates will also be presented. Willingness to pay for QALY gained will assumed to be in the range £20,000-£30,000 as per NICE guidance.

27.4.3. iFIT1 Exploratory endpoints

Investigation into infection interactions

Certain genetic characteristics and medical history are suspected to influence the incidence and rate of infections. These will be investigated under this endpoint including iVIG usage and vaccination history.

Infection risk prediction

The ability to predict prospectively which participants are most at risk of infections could support the implementation of novel immunotherapies in practice. This will be investigated under this endpoint.

28. iFIT1 TRIAL DESIGN

iFIT1 will assess whether escalating to daratumumab combined with TCE therapy (teclistamab or talquetamab) for 18 cycles improves PFS at 24 months compared to DRd to progression in patients who are MRD positive and FIT or UNFIT after 6 cycles of DRd as standard care. Eligible participants will be randomly allocated, using a minimisation algorithm with a random element, in a 1:1:1 ratio to receive DRd to progression (standard care), Dara-Tec for 18 cycles, or Dara-Tal for 18 cycles. A total of 652 participants are required to be randomised in order to reach the sample size for the powered comparisons.

29. iFIT1 PARTICIPANT ELIGIBILITY

Eligibility waivers to inclusion/exclusion criteria are not permitted.

Confirmation of eligibility for the **iFIT1** pathway must be recorded in the patient's notes. If a participant is not eligible for their assigned **iFIT1** pathway, they cannot continue in the trial at all, i.e., not under any pathway.

29.1. Trial randomisation – iFIT1 pathway

Participants must meet all of the following inclusion criteria and none of the exclusion criteria.

Each participant must only be randomised once.

29.1.1. Inclusion criteria for iFIT1 pathway

1. Completed 6 cycles of DRd induction therapy after registering within the iFIT study. Dexamethasone may have been stopped due to toxicity and the participant will remain eligible,
2. Planned to continue on at least daratumumab (monthly) and lenalidomide (at any dose level),
3. Achieved a partial response (PR) biochemically (irrespective of MRD status) or achieved a ≥VGPR and are MRD positive, as confirmed by HMDS,
4. Categorised as FIT or UNFIT according to the IMWG frailty index (see Appendix 48.3),
5. Able to provide full informed consent,
6. Prepared to comply with pregnancy prevention plan, and
7. Meet all of the following blood criteria within 14 days before randomisation:
   Haematological (if criteria not met at first test can be repeated):
   a) Absolute neutrophil count (ANC) ≥ 1 x 10^9/L. Unless the participant has a proven or presumed diagnosis of Duffy null phenotype neutropenia in which case an ANC ≥ 0.75 x 10^9/L is allowed. Without GCSF within the prior 5 days,
   b) Platelet count ≥ 50 x 10^9/L. Without platelet transfusion within the prior 7 days,
   c) Haemoglobin ≥ 80g/L. Without blood transfusion within the prior 7 days,
   Biochemical:
   d) Total bilirubin ≤ 3 x ULN, except in participants with congenital bilirubinaemia (Gilbert's Syndrome) in which case direct bilirubin ≤3 x ULN,
   e) Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3 x ULN, and
   f) Adequate renal function defined as estimated CrCl ≥ 30mL/min using Cockcroft-Gault formula.

29.1.2. Exclusion criteria for iFIT1 pathway

1. Received systemic anti-myeloma therapy other than DRd prior to randomisation. Steroids given (by any route) for reasons other than myeloma disease control are allowed,
2. Received a stem cell transplant,
3. Stable disease (SD) or progressive disease (PD) as per IMWG response criteria (see Appendix 48.2),
4. A history of any other active malignancy diagnosed within 2 years prior to randomisation, except for:
   a. Non-invasive bladder cancer (solitary papillary urothelial neoplasm of low malignant potential (Ta-PUN-LMP) or low grade, <3cm, no carcinoma *in-situ*,
   b. Adequately treated basal cell or squamous cell skin cancer, or localised melanoma treated with curative surgical resection alone,
   c. Breast cancer: adequately treated lobular carcinoma in situ or ductal carcinoma in situ or history of localised breast cancer (anti hormonal treatment is permitted),
   d. Localised prostate cancer (M0N0) with a Gleason score of ≤7a, treated locally only,
   e. Non-invasive cervical cancer, or
   f. Other malignancy that is considered cured (must be discussed with the CIs),
5. Major surgery within 14 days before randomisation. This does not include vertebroplasty or kyphoplasty,
6. Evidence of central nervous system involvement by myeloma at the time of randomisation. If suspected, an MRI +/- lumbar puncture is required to investigate,
7. Stroke, transient ischemic attack or seizure within 6 months of randomisation,
8. Contraindications, hypersensitivity or intolerance to any proposed treatment or its excipients,

9. Pregnant, breast feeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within 5 months after the last dose,
10. Received a live attenuated vaccine within 4 weeks of randomisation,
11. Active systemic viral fungal or bacterial infection requiring systemic therapy. Criteria for specific chronic infections clarified below:
    a. Participants with HIV can participate after discussion with the chief investigators unless they meet the following criteria:
        i. History of AIDS-defining illness,
        ii. CD4 count <350 cells/mm3 at screening,
        iii. Detectable viral load during screening or within 6 months prior to screening,
        iv. Not receiving ART,
        v. Had a change in antiretroviral therapy within 6 months, or
        vi. Receiving antiretroviral therapy that may interfere with study drugs,
    b. Participants with evidence of Hepatitis B infection AND Hepatitis B sAg or HBV-DNA positive at the time of screening. Participants with Hepatitis B core antibody positivity must undergo HBV-DNA testing,
    c. Active Hepatitis C as measured by positive HCV RNA. Participants with a history of HCV antibody positive must undergo HCV-RNA testing. If a participant has prior Hepatitis C and has completed antiviral therapy and has undetectable HCV-RNA ≥12 weeks following the completion of therapy they are eligible,
12. Significant cardiac co-morbidity:
    a. New York Heart Associate stage III or IV congestive cardiac failure,
    b. Myocardial infarction, unstable angina or coronary artery bypass graft within 6 months of commencing allocated **iFIT1** treatment,
    c. History of clinically significant ventricular arrythmia or unexplained syncope (unless thought to be vasovagal), or
    d. Uncontrolled cardiac arrythmia or clinically significant electrocardiogram abnormalities without prior investigation/management,
13. Significant respiratory co-morbidity:
    a. Active diffuse infiltrative pulmonary disease,
14. Active autoimmune disease requiring systemic immunosuppressive therapy within 6 months before start of study treatment. Except: vitiligo, controlled type 1 diabetes, prior autoimmune thyroid disease but currently euthyroid – regardless of when these were diagnosed,
15. Disabling psychiatric conditions, severe dementia, altered mental status or any other conditions that the investigator considers would put the participant at an increased risk of participation, or
16. Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring.

30. iFIT1 TRIAL PROCEDURES

The following section should be consulted in line with Section 18.

30.1. Non-randomisation

For participants who do not undergo **iFIT1** randomisation, the reason should be recorded on the applicable eCRF.

Reasons for non-randomisation will be monitored by the CTRU alongside recruitment progress.

30.2. iFIT1 trial randomisation system

iFIT1 randomisation will be performed using the CTRU automated 24-hour web-based system. An authorised PIN will be required for first time users to access the system. They will be provided by the CTRU to staff approved to use the system by the PI on the trial APL, after the research site has received formal approval to open to recruitment. Existing users will access the system using their email and personal password. All registrations and randomisations can be accessed using the following link: https://lictr.leeds.ac.uk/webrand/.

Care must be taken to ensure the correct "randomisation pathway" (iFIT1), site code, and trial ID are selected/entered to ensure correct randomisation into iFIT1.

30.3. iFIT1 randomisation

30.3.1. Consent for iFIT1 randomisation

Once it is known that the participant will be assigned to the **iFIT1** randomisation pathway (expected to be *around* standard of care induction cycle 6 day 28), the potential participant will be provided with a full verbal explanation of the **iFIT1** treatment pathway and be given the **iFIT1** PISICD to consider. It is the responsibility of the research site to ensure that the participant still has a copy of the Study Registration PIS and Additional Information PIS to refer to. Following information provision, participants will be given the opportunity to further discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to continue their participation in the trial. The right of a participant to refuse to continue their participation in the trial without giving reasons must be respected.

Participants wishing to continue their participation in their assigned **iFIT1** pathway will be required to provide full informed consent using the **iFIT1** ICD.

30.3.2. Eligibility and assessments prior to iFIT1 randomisation

Upon completion of 6 cycles of standard of care induction, after confirmation from CTRU re randomisation pathway assignment, and within 14 days prior to **iFIT1** randomisation, the following local investigations and assessments must be performed to confirm eligibility for randomisation. If randomisation does not occur within 14 days of the assessments following the end of standard of care induction, repeat local investigations and assessments will be required to confirm eligibility.

There must be no break in treatment of more than 6 weeks from cycle 6 day 28 of standard of care induction. If treatment is delayed after cycle 6 day 28 for 6 weeks or more, the participant will be considered as off-trial unless discussed and agreed with the CIs, after which point further treatment will be at the discretion of the treating clinician.

Local investigations prior to randomisation

- Review of medical history in line with eligibility criteria for **iFIT1** (including other previous malignancies),
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine,
- Hepatitis B (surface antigen and core antibody), hepatitis C and HIV. PCR for active infection should be conducted if any of the antibody tests listed here are positive,
- Assessment of cardiac risk, and

- Calculated CrCl (CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospital is not accurate is older patients).

30.3.3. iFIT1 randomisation

Full informed consent for continuation in the trial in the **iFIT1** pathway must be obtained prior to randomisation.

Once participants have given full informed consent and are confirmed eligible, they can be randomised. The participant will continue to use the same trial number as allocated to them at registration.

The following information will be required at randomisation:

- Name of person performing the randomisation,
- Research site name and site code,
- Trial ID number (as allocated at registration),
- Participant details, including initials, date of birth and NHS/CHI number,
- Confirmation of eligibility,
- Confirmation of full informed consent, and
- Email address and/or phone number of participants who choose to complete questionnaires online.

Care must be taken to ensure the correct "randomisation pathway" (iFIT1), site code, and trial ID are selected/entered to ensure correct randomisation into iFIT1.

24-hour iFIT1 randomisation:

https://lictr.leeds.ac.uk/webrand/

Following randomisation, completed **iFIT1** consent forms must be sent via the CTRU Secure File Transfer Service or other CTRU-approved method (never standard e-mail).

Automated confirmation of **iFIT1** randomisation will be emailed to the research site team. The local hospital will provide each participant with a trial ID card, which they should carry with them at all times and present to medical staff should they be admitted to hospital during their time on the trial. Eligibility for **iFIT1** treatment must be confirmed on the applicable eCRF before **iFIT1** treatment can start.

The research site team should notify the participant's GP that they are continuing to take part in the trial under the **iFIT1** pathway using the approved template letter provided by the CTRU. A copy of the letter should be filed in the ISF.

Participants will be randomly allocated on a 1:1:1 basis to receive either:

- Continue DRd therapy until PD,
- Dara-Tec for 18 cycles and then active monitoring until PD, or
- Dara-Tal for 18 cycles and then active monitoring until PD.

A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Trial site,
- IMWG frailty group at the end of DRd induction (FIT, UNFIT),
- R2-ISS stage at registration (Stage I, Stage II, Stage III, Stage IV, unknown), and
- Response to DRd induction (≥VGPR, <VGPR).

The IMWG frailty group, R2-ISS stage, and response to DRd induction will not be entered by research site staff at the point of randomisation. However, the appropriate eCRFs relating to the end of standard of care induction must have been previously completed in order for the participant to proceed to randomisation.

If participants are allocated to receive Dara-Tec or Dara-Tal, the local hospital will provide each participant with an iFIT-specific teclistamab or talquetamab **safety card**. The participant should carry this with them at all times and present to medical staff should they be admitted to hospital during their time on the trial.

30.4. iFIT1 trial assessments

Participants who are randomised to the Dara-Tec or Dara-Tal treatment arms, should continue to be assessed on a monthly basis after completion of 18 cycles (i.e., at the same timepoints as participants randomised to DRd) until disease progression. This is referred to as active monitoring.

A tabulated summary of all local and central assessments is provided in Appendix 48.6.

Please refer to the trial eCRFs to ensure you are familiar with all data collection items prior to completing assessments.

30.4.1. Local investigations at the start of each iFIT1 treatment/active monitoring cycle

Within the timeframe of day 1 (or within 5 days prior to day 1) of each treatment/active monitoring cycle, the following local investigations and assessments should be performed and documented on the applicable eCRF. Please refer to Section 31.6 for criteria for starting each cycle.

- Physical examination (including systolic and diastolic blood pressure, height, weight, vital signs (pulse, O2 saturation, respiratory rate, temperature), and an assessment of visual acuity as indicated, and symptom directed,
- Adverse events assessed by NCI-CTCAE V5 grades (see Section 20 and Appendix 48.5). If an infection is reported, then additional details, including e.g. results of blood cultures or viral PCR tests, if appropriate, will be required,
- Adverse events of special interest (CRS and ICANS) assessed, including reporting neurological examination and immune effector cell encephalopathy (ICE) score, before each step-up dose, each first maintenance dose, and on cycle 2 day 1 for participants receiving teclistamab and talquetamab,
- ECOG and Karnofsky performance status (See Appendix 48.4),
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, creatinine, CrCl, CRP, and total IgG. CrCl should be calculated using the Cockcroft-Gault formula, as the estimated GFR produced in most hospitals is not accurate in older patients.
- Serum paraprotein and immunofixation, SFLC and urinary monoclonal protein detection (quantification where available),
- An assessment of disease response according to the IMWG response criteria (see Appendix 48.2) is required at the end of each cycle of treatment. Samples for this assessment must be taken at, or ≤5 days prior to, cycle 1 day 1 of the next cycle to provide a response. Please note where participant has non-secretory disease adequate imaging and bone marrow sampling to monitor for response and disease progression must be performed,
- Pregnancy test for participants receiving lenalidomide. WCBP (see Appendix 48.10) receiving lenalidomide must have a negative pregnancy test performed by a healthcare

professional on day 1 (or ≤3 days prior) of each cycle of treatment (as per the pregnancy prevention plan for lenalidomide),
- Pregnancy prevention counselling for participants receiving lenalidomide,
- Infection prevention assessment, including vaccination history and prophylactic medications for infection given, and
- If at any point a first occurrence of CR or sCR is suspected, then it is recommended that a bone marrow aspirate and trephine is sent for local review as well as to HMDS (see Appendix 48.7). CR and sCR cannot be confirmed without bone marrow.

The following assessments are to be carried out for all participants <u>if clinically indicated (standard of care)</u>:

- Cross-sectional imaging according to local practice in accordance with IMWG recommendations for response assessment and NICE guidance and if clinically indicated (standard of care). For monitoring accepted methods include whole body low dose CT, MRI, or PET-CT. MRI spine/pelvis alone is insufficient and should be supplemented by a whole body technique, e.g., whole body low dose CT. Additional imaging is not required by the trial protocol,
- Assessment of cardiac risk, only if clinically indicated as part of standard care, and
- Thyroid function monitoring, only if clinically indicated as part of standard care.

30.4.2. Frailty assessments

Frailty assessments will be carried out for all participants until progression or withdrawal from trial treatment/active monitoring at the following timepoints post-randomisation:

- After 6 cycles of **iFIT1** treatment,
- After 12 cycles of **iFIT1** treatment,
- After 18 cycles of **iFIT1** treatment,
- After 24 cycles of **iFIT1** treatment/after 6 cycles of active monitoring,
- After 30 cycles of **iFIT1** treatment/after 12 cycles of active monitoring, and
- After 36 cycles of **iFIT1** treatment/after 18 cycles of active monitoring.

The frailty assessments to be carried out post-randomisation are as follows:

- IMWG frailty index (Charlson Comorbidity Score, ADL, and IADL – Appendix 48.3), and
- ECOG and Karnofsky performance status (Appendix 48.4).

See Section 22.1 regarding source data for these assessments.

30.4.3. Quality of life (QoL) and healthcare resource use questionnaires

Participants will be asked to complete questionnaires at 3, 6, 12, 18, 24, and 30 months post-randomisation. See Section 18.11 for further information.

30.4.4. Central investigations

The following samples should be taken and sent to the following organisations at the specified timepoints.

- <u>HMDS:</u> Bone marrow aspirate (5mL) in EDTA for MRD:
  - After 18 cycles of **iFIT1** treatment, and
  - After 30 cycles of **iFIT1** treatment/after 12 cycles of active monitoring,

- RMH/ICR:
    - Bone marrow aspirate (5mL) in EDTA for translational work:
        - After 18 cycles of **iFIT1** treatment **(first 300 participants only – we will tell research site teams when to stop sending this sample)**, and
        - At progression,
    - Peripheral blood sample (20mL) in EDTA for translational work **and** clotted blood sample (10mL) in EDTA for translational work:
        - After 6 cycles of **iFIT1** treatment,
        - After 18 cycles of **iFIT1** treatment,
        - After 30 cycles of **iFIT1** treatment/after 12 cycles of active monitoring, and
        - At progression.

30.5. Treatment discontinuation after randomisation

Participants are only considered to be off-trial if:

- They have stopped receiving all trial IMPs when they are expected to receive the trial IMPs, or
- They have withdrawn from active monitoring.

If they are still receiving at least one trial IMP, or have not withdrawn from active monitoring, they are considered on-trial.

Participants that discontinue trial treatment following randomisation and before the end of active follow-up will still attend/complete the following assessments until disease progression:

- 2 monthly follow-up to include the local investigations listed in Section 30.4.1,
- Central investigations (see Section 30.4.4), and
- QoL/healthcare resource use questionnaires (see Section 30.4.3).

See Section 18.19 if the treatment discontinuation is due to participant withdrawal. The participant may withdraw from the assessments listed above in addition to the trial treatment.

See Section 18.15 if the treatment discontinuation is due to disease progression.

See Section 18.16 for post-progression follow-up.

30.6. Collection and use of email address and/or telephone number

Should participants choose to complete questionnaires online post-randomisation, their email address and/or telephone number will be collected dependent on the method by which they choose to receive the questionnaires (email and/or text). This information will be stored securely at the CTRU separate to all other iFIT trial data.

31. iFIT1 TRIAL TREATMENTS

Please refer to the iFIT Pharmacy and IMP Management SSOP for full details of the trial IMP management requirements including IMP ordering, destruction, accountability and disposal records.

Participants are randomised to one of the following arms within **iFIT1**:

- Continue DRd until PD,

- Dara-Tec for 18 cycles, then enter a period of active monitoring until PD, **OR**
- Dara-Tal for 18 cycles, then enter a period of active monitoring until PD.

The below are classed as IMPs during **iFIT1** if randomised to receive Dara-Tec or Dara-Tal.

If randomised to continue DRd in **iFIT1**, refer to Section 19 for the daratumumab, lenalidomide and dexamethasone IMPs. Daratumumab should be reduced to once a month, in line with standard of care.

31.1. Name and description of daratumumab, teclistamab and talquetamab for the Dara-Tec and Dara-Tal combinations

31.1.1. Daratumumab

Trade name: DARZALEX

Composition: Daratumumab is supplied as a clear to opalescent, colourless to yellow, solution for injection. Daratumumab will be provided in 15mL vials with elastomeric closures. Each 15mL vial contains a nominal content of 1,800mg of daratumumab.

The solution contains the following excipients: water for injection, recombinant human hyaluronidase, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20 and sorbitol.

31.1.2. Teclistamab

Trade name: TECVAYLI

Composition: Teclistamab is supplied as a colourless to light yellow solution for injection. Teclistamab will be provided in 3mL and 1.7mL vials with elastomeric closures. Each 3mL vial contains a nominal content of 30mg of teclistamab. Each 1.7mL vial contains a nominal content of 153mg of teclistamab.

The pH of the solution is 5.2. The solution contains the following excipients: water for injection, EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate and sucrose.

31.1.3. Talquetamab

Trade name: TALVEY

Composition: Talquetamab is supplied as a colourless to light yellow solution for injection. Talquetamab will be provided in 1.5mL and 1mL vials with elastomeric closures. Each 1.5mL vial contains a nominal content of 3mg of talquetamab (2mg/mL). Each 1mL vial contains a nominal content of 40mg of talquetamab (40mg/mL).

The pH of the solution is 5.2. The solution contains the following excipients: water for injection, EDTA disodium salt dihydrate, glacial acetic acid, polysorbate 20, sodium acetate trihydrate and sucrose.

31.2. Regulatory status of daratumumab, teclistamab and talquetamab

Daratumumab, teclistamab and talquetamab each have a MA in the UK. The use of daratumumab in combination with either teclistamab or talquetamab is outside of the daratumumab MA. The use of teclistamab/talquetamab in combination with daratumumab and the dosing schedule is outside of the teclistamab/talquetamab MA.

31.3. Product characteristics of daratumumab, teclistamab and talquetamab

The SmPC will be used for daratumumab, teclistamab and talquetamab.

CTRU will supply research sites with the SmPCs for the purposes of pharmacovigilance reporting (for determining causality of an event). This is not necessarily the most recent available version online.

31.4. Drug storage and supply of daratumumab, teclistamab and talquetamab for Dara-Tec and Dara-Tal combinations

Daratumumab, teclistamab and talquetamab will be supplied solely for use in this trial by Johnson & Johnson Innovative Medicine free of charge. Daratumumab is only supplied in the Dara-Tec and Dara-Tal TCE combination arms. Research sites must ring-fence the daratumumab, teclistamab and talquetamab upon receipt as outlined in the iFIT Pharmacy and IMP Management SSOP. Refer to the iFIT Pharmacy and IMP Management SSOP for daratumumab (Dara-Tec and Dara-Tal TCE combination arms only), teclistamab and talquetamab ordering procedures.

Storage of IMPs are in line with the manufacturers' recommendations. For further details please refer to the SmPC for each IMP.

Full accountability of trial-supplied daratumumab (Dara-Tec and Dara-Tal TCE combination arms only), teclistamab and talquetamab must be recorded on the trial-specific accountability logs within the PSF.

A product quality complaint PQC is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Study site personnel must report all PQCs to CTRU within 24 hours of becoming aware of the event as detailed in the iFIT Pharmacy and IMP Management SSOP. Whenever possible, the associated product should be retained in accordance with the label instructions pending further guidance from the relevant pharmaceutical company. A sample of the suspected product should be retained for further investigation, if requested.

31.5. Preparation and labelling of daratumumab, teclistamab and talquetamab

Daratumumab (for Dara-Tec and Dara-Tal arms only), teclistamab and talquetamab supplies will contain an annex 13 compliant study-specific label in line with Directive 2001/20/EC and the Medicines for Human Use (Clinical Trials) Regulations 2004 (amended 2006). Local pharmacy will be responsible for completing individual participant details on each label.

31.6. Routine tests before each cycle of Dara-Tec and Dara-Tal treatment

At day 1 (or ≤5 days prior to each cycle) prior to treatment being given, participants will be assessed for their suitability for treatment. Following a break in treatment, assessment of suitability must still be carried out at day 1 (or ≤5 days prior to treatment re-commencing). Please see Section 30.4.1 for details of assessments to be performed.

For a new cycle of treatment to begin, the participant must meet the following criteria within the assessments performed as part of standard clinical care (day 1 or ≤5 days prior):

<u>Haematological:</u>

- ANC must be ≥ 1.0 x 10^9/L. Unless the participant has a proven or presumed diagnosis of Duffy null phenotype neutropenia in which case an ANC ≥ 0.75 x 10^9/L is allowed. GCSF support is allowed,

- Platelet count must be ≥ 50 x 10^9/L, platelet transfusions are not allowed ≤3 days prior to assessment, and
- Haemoglobin ≥ 80 g/L. The use of red blood cell transfusions is permitted.

Biochemical:

- Total bilirubin ≤ 3 x ULN, except in participants with congenital bilirubinaemia (Gilbert's Syndrome) in which case direct bilirubin ≤3 x ULN, and
- Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN.

Non-haematologic toxicity related to study drugs (except for alopecia) must have resolved to grade 1 or less or to the participant's baseline condition, or to a severity level considered stable and tolerable by the investigator/participant, and in the opinion of the investigator safe to resume treatment.

If the participant fails to meet the above-cited criteria for initiation of the next cycle of treatment dosing should be delayed for 1 week. At the end of that time, the participant should be re-evaluated to determine whether the criteria have been met. If the participant continues to fail to meet the above-cited criteria, the treatment should be delayed and continue to be re-evaluated. The maximum delay caused by failure to meet the above criteria before treatment should be discontinued will be 3 weeks or at the discretion of the CIs after consultation. The maximum time before being considered off-trial will be 6 weeks unless discussed and agreed with the CIs.

Where treatment has been delayed for 3 weeks or more (regardless of the reason and not including between date of randomisation and cycle 1 day 1), then treatment cannot be (re)commenced without approval of the CIs (via the CTRU). If the delay is less than 3 weeks, then it is up to the treating clinician to determine. This also applies to delays mid-way through a cycle.

See Section 31.8 for information on dose modifications and delays.

Cardiac risk should be assessed and appropriately managed and monitored throughout treatment.

Thyroid function should be monitored regularly as per local standard of care.

31.7. Dosage schedules for Dara-Tec and Dara-Tal

Refer to Section 19.8 for DRd.

31.7.1. Dara-Tec

Daratumumab will be administered via SC injection over approximately 3 to 5 minutes for a total of 18 cycles. Each cycle is 28 days.

Table 9: Dosage schedule for daratumumab for participants receiving Dara-Tec

iFIT1 cycle		Dose	Days
1-18		1800mg	1

Teclistamab will be administered via SC injection for a total of 18 cycles. Each cycle is 28 days.

Table 10: Dosage schedule for teclistamab for participants receiving Dara-Tec

iFIT1 cycle	Step-up/treatment	Dose[a]	Days
1 (step-up dosing schedule)	Step-up 1	0.06mg/kg	1*
	Step-up 2	0.3mg/kg	3[b]
	First maintenance dose	1.5mg/kg	8[c]
1	Second maintenance dose	1.5mg/kg	15[d]

2-18	Subsequent maintenance doses	3mg/kg	1[e]*

[a] Dose is based on the participant's weight taken on Day 1 of Cycle 1 of **iFIT1** treatment (or ≤5 days prior). Dosing should be reviewed based on the weight taken prior to Day 1 of each subsequent cycle (or ≤5 days prior) and adjusted if there is a >10% change from the weight used for the initial calculation. The dose should be administered subcutaneously. Dose banding is shown in Appendix 48.14.
[b] Step-up 2 can occur 2-7 days after Step-up 1.
[c] First maintenance dose can occur 2-7 days after Step-up 2.
[d] There must be at least 5 days between the two first maintenance doses.
[e] There must be at least 12 days between the second maintenance dose and the start of cycle 2.
*On days when both daratumumab and teclistamab are administered, teclistamab should be administered >1 hour after daratumumab.

Teclistamab must not be administered within 7 days of receiving lenalidomide.

Teclistamab vials of different concentrations should not be combined to achieve maintenance dose.

No dose adjustments are recommended based on age, renal or hepatic impairment.

Participants must be admitted for observation or instructed to remain within proximity of a healthcare facility and monitored daily for 48 hours after administration of all doses within the teclistamab step-up phase for signs and symptoms of CRS and immune effector cell-associated neurotoxicity syndrome (ICANS). Safety bloods (including FBC, coagulation, U&Es, and LFTs) should be repeated before each dose and doses delayed in the event of toxicity, as per Table 15.

These precautions must be followed when participants are:

- Receiving each step-up dose and the first 1.5mg/kg dose of teclistamab, or
- Receiving teclistamab after experiencing grade 2 or higher CRS.

During this time tocilizumab must be immediately available within the clinical area to which the participant is admitted or will first present is being managed through an ambulatory protocol.

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. However, treatment for CRS should not be delayed. Cultures and imaging should be obtained; the clinical signs and symptoms should determine which tests are appropriate.

To minimise the risk of CRS, all participants treated with teclistamab must receive the pre-treatment, as outlined in the table below, 1 to 3 hours prior to receiving each step-up dose and the first full dose of teclistamab in the step-up schedule.

Table 11: Teclistamab pre-treatment for participants receiving Dara-Tec

Drug	Dose	Route
Dexamethasone	16mg	Oral or IV
Chlorphenamine	4mg or 10mg	Oral or IV
Paracetamol	1g	Oral or IV

If patients were continuing to receive pre-medications for daratumumab due to prior IRR at the end of the induction DRd cycles then these pre-medications (including montelukast if needed) should be given before daratumumab administration. In this case:

- If more than 3 hours elapse between their administration and teclistamab dosing, then an additional dose of dexamethasone 8mg must be given (at least 15 minutes prior to teclistamab dosing), or
- If more than 6 hours elapse between their administration and teclistamab dosing then an additional dose of dexamethasone 8mg, chlorphenamine and paracetamol (doses as above) must be given (at least 30 mins prior to teclistamab dosing).

Administration of pre-treatment medicinal products may also be required prior to administration of subsequent doses of teclistamab for patients who:

- Repeat doses within the teclistamab step-up dosing schedule due to dose delays,
- Experienced CRS following the previous dose, or
- Were continuing to receive pre-medications prior to DRd at the end of induction (in this case pre-treatment for prophylaxis of IRR with daratumumab should continue).

31.7.2. Dara-Tal

Daratumumab will be administered via SC injection over approximately 3 to 5 minutes for a total of 18 cycles. Each cycle is 28 days.

Table 12: Dosage schedule for daratumumab for participants receiving Dara-Tal

iFIT1 cycle	Dose	Days
1-18	1800mg	1

Talquetamab will be administered via SC injection for a total of 18 cycles. Each cycle is 28 days.

Table 13: Dosage schedule for talquetamab for participants receiving Dara-Tal

iFIT1 cycle	Step-up/treatment	Dose[a]	Days
1 (step-up dosing schedule)	Step-up 1	0.01mg/kg	1*
	Step-up 2	0.06mg/kg	3[b]
	Step-up 3	0.4mg/kg	8[c]
	First maintenance dose	0.8mg/kg	15[d]
2-6	Maintenance doses	0.8mg/kg	1[e]* and 15[f]
7-18	Maintenance doses	0.8mg/kg	1*

[a] Dose is based on the participant's weight taken on Day 1 of Cycle 1 of **iFIT1** treatment (or ≤5 days prior). Dosing should be reviewed based on the weight taken prior to Day 1 of each subsequent cycle (or ≤5 days prior) and adjusted if there is a >10% change from the weight used for the initial calculation. The dose should be administered subcutaneously. Dose banding is shown in Appendix 48.14.
[b] Step-up 2 can occur 2-7 days after Step-up 1.
[c] Step-up 3 can occur 2-7 days after Step-up 2.
[d] First maintenance dose can occur 2-7 days after Step-up 3.
[e] There must be at least 12 days between the first maintenance dose and the first maintenance dose in cycle 2.
[f] Day 15 of cycle 2-6 can be adjusted +/- 3 days, provided talquetamab doses remain at least 12 days apart.
*On days when both daratumumab and talquetamab are administered, talquetamab should be administered >1 hour after daratumumab.

Talquetamab must not be administered within 7 days of receiving lenalidomide.

Dose banding shown in Appendix 48.14.2. Talquetamab vials of different concentrations should not be combined to achieve maintenance dose.

Participants must be admitted for observation or instructed to remain within proximity of a healthcare facility and monitored daily for 48 hours after administration of all doses within the talquetamab step-up phase for signs and symptoms of CRS and ICANS. Safety bloods (including FBC, coagulation, U&Es, and LFTs) should be repeated before each dose and doses delayed in the event of toxicity as per Table 17.

These precautions must also be followed when participants are:

- Receiving each step-up dose and the first 0.8mg/kg dose of talquetamab, or
- Receiving talquetamab after experiencing grade 2 or higher CRS.

During this time tocilizumab must be immediately available within the clinical area to which the participant is admitted or will first present if being managed through an ambulatory protocol.

Infection and CRS may have a similar presentation. Therefore, investigators are strongly encouraged to evaluate for an infection at the first signs or symptoms of CRS. However, treatment for CRS should not be delayed. Cultures and imaging should be obtained; the clinical signs and symptoms should determine which tests are appropriate.

To minimise the risk of CRS, all participants treated with talquetamab should receive the pre-treatment, as outlined in the table below, 1 to 3 hours prior to each dose during the step-up phase:

Table 14: Talquetamab pre-treatment for participants receiving Dara-Tal

Drug	Dose	Route
Dexamethasone	16mg	Oral or IV
Chlorphenamine	4mg or 10mg	Oral or IV
Paracetamol	1g	Oral or IV

If patients were continuing to receive pre-medications for daratumumab due to prior IRR at the end of the induction DRd cycles, then these pre-medications (including montelukast if needed) should be given before daratumumab administration. In this event:

- If more than 3 hours elapse between their administration and talquetamab dosing, then an additional dose of dexamethasone 8mg must be given (at least 15 minutes prior to talquetamab dosing), or
- If more than 6 hours elapse between their administration and talquetamab dosing then an additional dose of dexamethasone 8mg, chlorphenamine, and paracetamol (doses as above) must be given (at least 30 minutes prior to talquetamab dosing).

Administration of pre-treatment medicinal products may also be required prior to administration of subsequent doses of talquetamab for patients who:

- Repeat doses within the teclistamab step-up dosing schedule due to dose delays,
- Experienced CRS following the previous dose, or
- Were continuing to receive pre-medications prior to DRd at the end of induction (in this case pre-treatment for prophylaxis of IRR with daratumumab should continue).

31.8. Dosage modifications for Dara-Tec and Dara-Tal

Refer to Section 19.9 for DRd.

Once a participant receives their day 1 treatment of a cycle this is classed as a cycle, and the cycle should last at least 28 days. If administrative reasons, e.g., bank holiday closures, necessitate a delay

to the start of the subsequent cycle, then up to a week delay is permitted. This would also be acceptable for participants requesting breaks to go on holiday. Delays of longer than one week must be discussed with the CIs via the CTRU.

31.8.1. Dara-Tec

No dose reductions of daratumumab or teclistamab are recommended. Dose delay may be required to allow recovery after adverse events or of blood cell counts in the event of haematological toxicity (see below).

Table 15: Recommended actions taken after adverse reactions following administration of Dara-Tec

Adverse reaction	Grade	Actions
Cytokine release syndrome (CRS)[a]	Grade 1 • Temperature ≥ 38°C[b]	• Withhold teclistamab until adverse reaction resolves. • See Table 19 for management of CRS. • Administer pre-treatment medicinal products prior to next dose of teclistamab.
	Grade 2 • Temperature ≥ 38°C[b] with either: o Hypotension responsive to fluids and not requiring vasopressors, or o Oxygen requirement of low-flow nasal cannula[c] or blow-by Grade 3 (Duration: less than 48 hours) • Temperature ≥ 38°C[b] with either: o Hypotension requiring one vasopressor with or without vasopressin, or o Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask	• Withhold teclistamab until adverse reaction resolves. • See Table 19 for management of CRS. • Administer pre-treatment medicinal products prior to next dose of teclistamab. • Monitor patient daily for 48 hours following the next dose of teclistamab. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent or duration: more than 48 hours) • Temperature ≥ 38°C[b] with either: o Hypotension requiring one vasopressor with or without vasopressin, or o Oxygen requirement of high-flow nasal cannula[c], facemask, non-rebreather mask, or Venturi mask. Grade 4 • Temperature ≥ 38°C[b] with either:	• Permanently discontinue therapy with teclistamab. • See Table 19 for management of CRS.

	○ Hypotension requiring multiple vasopressors (excluding vasopressin), or ○ Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation).	
Immune effector cell-associated neurotoxicity syndrome (ICANS)[d]	Grade 1	• Withhold teclistamab until adverse reaction resolves. • See Table 20 for management of ICANS.
	Grade 2 Grade 3 (First occurrence)	• Withhold teclistamab until adverse reaction resolves. • See Table 20 for management of ICANS. • Monitor patient daily for 48 hours following the next dose of teclistamab. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue therapy with teclistamab. • See Table 20 for management of ICANS.
Infections	All grades	• Do not administer teclistamab step-up dosing schedule in patients with active infection. Teclistamab step-up dosing schedule may proceed upon resolution of active infection.
	Grade 2 Grade 3 Grade 4	• Withhold subsequent maintenance doses of teclistamab and daratumumab (i.e., doses administered after teclistamab step-up dosing schedule) until infection improves to grade 1 or better.
Haematologic toxicities	Absolute neutrophil count less than 0.5×10^9/L	• Withhold teclistamab and daratumumab until absolute neutrophil count is 0.5×10^9/L or higher. Consider commencing GCSF except in the setting of active CRS.
	Febrile neutropenia	• Withhold teclistamab and daratumumab until absolute neutrophil count is 1.0×10^9/L or higher, and fever resolves. Consider commencing GCSF

		except in the setting of active CRS.
	Platelet count less than 25 x 10^9/L Platelet count between 25 x 10^9/L and 50 x 10^9/L with bleeding	• Withhold teclistamab and daratumumab until platelet count is 25 x 10^9/L or higher and no evidence of bleeding.
Other adverse reactions[e]	Grade 3 Grade 4	• Withhold teclistamab and daratumumab until adverse reaction improves to grade 2 or better. If toxicity clearly attributable to one agent only then the other can be continued.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) grading for CRS (Lee et al 2019).
[b] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids).
[c] Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min.
[d] Based on ASTCT grading for ICANS.
[e] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), V5.

Recommendations on restarting teclistamab after a dose delay are as follows:

Table 16: Recommendations for restarting teclistamab after a dose delay

Last dose administered	Duration of delay from the last dose administered	Action
Step-up dose 1	More than 7 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06mg/kg)
Step-up dose 2	8 days to 28 days	Repeat step-up dose 2 (0.3mg/kg) and continue teclistamab step-up dosing schedule
	More than 28 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06mg/kg)
Any maintenance doses	8 days to 62 days	Continue teclistamab at last maintenance dose and schedule
	63 days to 111 days	Restart teclistamab step-up dosing schedule at step-up dose 2 (0.3mg/kg)
	More than 111 days	Restart teclistamab step-up dosing schedule at step-up dose 1 (0.06mg/kg)

31.8.2. Dara-Tal

No dose reductions of daratumumab or talquetamab are recommended. Dose delay may be required to allow recovery after adverse events or of blood cell counts in the event of haematological toxicity (see below).

Table 17: Recommended actions taken after adverse reactions following administration of Dara-Tal

Adverse reaction	Severity	Dose modification
Cytokine release syndrome (CRS)[a]	Grade 1 • Temperature ≥ 38°C[b]	• Withhold talquetamab until CRS resolves. • See Table 19 for management of CRS. • Administer pre-treatment medicinal products prior to next dose of talquetamab.
	Grade 2 • Temperature ≥ 38°C[b] with either: ○ Hypotension responsive to fluids and not requiring vasopressors, or ○ Oxygen requirement of low-flow nasal cannulac or blow-by Grade 3 (Duration: less than 48 hours) • Temperature ≥ 38°C[b] with either: ○ Hypotension requiring one vasopressor with or without vasopressin, or ○ Oxygen requirement of high-flow nasal cannulac, facemask, non-rebreather mask, or Venturi mask	• Withhold talquetamab until CRS resolves. • See Table 19 for management of CRS. • Administer pre-treatment medicinal products prior to next dose of talquetamab. • Monitor patient daily for 48 hours following the next dose of talquetamab. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent or duration more than 48 hours): • Temperature ≥ 38°C[b] with either: ○ Hypotension requiring one vasopressor with or without vasopressin, or ○ Oxygen requirement of high-flow nasal cannulac, facemask, non-rebreather mask, or Venturi mask. Grade 4 • Temperature ≥ 38°C[b] with either: ○ Hypotension requiring multiple vasopressors (excluding vasopressin), or ○ Oxygen requirement of positive pressure (e.g., continuous positive airway	• Permanently discontinue talquetamab. See Table 19 for management of CRS.

	pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation).	
Immune effector cell-associated neurotoxicity syndrome (ICANS)[d]	Grade 1	• Withhold talquetamab until ICANS resolves. • See Table 20 for management of ICANS.
	Grade 2 Grade 3 (First occurrence)	• Withhold talquetamab until ICANS resolves. • See Table 20 for management of ICANS. • Monitor patient daily for 48 hours following the next dose of talquetamab. Instruct patients to remain within proximity of a healthcare facility during daily monitoring.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue therapy with talquetamab. • See Table 20 for management of ICANS.
Infections	All grades	• Do not administer talquetamab step-up dosing schedule in patients with active infection. • Withhold talquetamab in the step-up phase until infection resolves.
	Grade 2 Grade 3 Grade 4	• Withhold subsequent maintenance doses of talquetamab and daratumumab (i.e., doses administered after talquetamab step-up dosing schedule) during the treatment phase until infection improves to grade 1 or better.
Haematologic toxicities	Absolute neutrophil count less than 0.5×10^9/L	• Withhold talquetamab and daratumumab until absolute neutrophil count is 0.5×10^9/L or higher. Consider commencing GCSF except in the setting of active CRS.
	Febrile neutropenia	• Withhold talquetamab and daratumumab until absolute neutrophil count is 1.0×10^9/L or higher, and fever resolves. Consider commencing GCSF except in the setting of active CRS.

	Platelet count less than 25 x 10^9/L Platelet count between 25 x 10^9/L and 50 x 10^9/L with bleeding	• Withhold talquetamab and daratumumab until platelet count is 25 x 10^9/L or higher and no evidence of bleeding.
Oral toxicity, including weight loss	Toxicity not responding to supportive care	Interrupt talquetamab until stabilisation or improvement, and consider restarting on modified schedule as follows: • If current dose is 0.8mg/kg every two weeks, change to 0.8mg/kg every four weeks. • If current dose is 0.8mg/kg every four weeks, change to 0.8mg/kg every eight weeks.
Skin reactions, including nail disorders	Grade 3 Grade 4	• Withhold talquetamab until adverse reaction improves to grade 1 or baseline.
Other non-haematologic adverse reactions[a]	Grade 3 Grade 4	• Withhold talquetamab and daratumumab until adverse reaction improves to grade 2 or baseline. • If toxicity clearly attributable to one agent only then the other can be continued.
[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), V5.		

Dose delays may be required to manage toxicities related to talquetamab. Recommendations on restarting talquetamab after a dose delay are as follows:

Table 18: Recommendations for restarting talquetamab after a dose delay

Last dose administered	Duration of delay from the last dose administered	Action
0.01mg/kg	More than 7 days	Restart at 0.01mg/kg
0.06mg/kg	8 days to 28 days	Repeat 0.06mg/kg
	More than 28 days	Restart at 0.01mg/kg
0.4mg/kg	8 days to 35 days	Repeat 0.4mg/kg
	36 days to 56 days	Restart at 0.06mg/kg
	More than 56 days	Restart at 0.01mg/kg
0.8mg/kg	14 days to 35 days	Repeat 0.8mg/kg
	36 days to 56 days	Restart at 0.4mg/kg
	More than 56 days	Restart at 0.01mg/kg

31.9. Known daratumumab, teclistamab, and talquetamab reactions and interaction with other therapies

31.9.1. Daratumumab

As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high

affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Daratumumab solution for SC injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 8% (95/1183) of patients experienced an IRR. Most IRRs occurred following the first injection and were grade 1-2. IRRs occurring with subsequent injections were seen in 1% of patients.

The median time to onset of IRRs following daratumumab injection was 3.2 hours (range 0.15 to 83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritus, chills, vomiting, nausea, hypotension and blurred vision. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, tachycardia and ocular adverse reactions (including choroidal effusion, acute myopia and acute angle closure glaucoma).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections.

Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g., short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease.

Management of IRRs related to daratumumab:
If an IRR develops during daratumumab SC administration, then the administration should be temporarily interrupted. Participants who experience AEs during daratumumab SC administration must be treated for their symptoms. Participants should be treated with paracetamol, antihistamine, or corticosteroids, as needed. IV saline may be indicated. For bronchospasm, urticaria, or dyspnea, participants may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, participants may require vasopressors. If ocular symptoms (including choroidal effusion, acute myopia, and acute angle-closure glaucoma) occur, interrupt daratumumab and seek immediate ophthalmologic evaluation prior to restarting daratumumab. In the event of recurrent grade 3 IRR (or grade 2 event for laryngeal oedema or bronchospasm) or a single life-threatening IRR (which may include pulmonary or cardiac events) or an anaphylactic reaction, daratumumab SC should be discontinued.

Interference with indirect antiglobulin test (indirect Coombs test):
Daratumumab binds to CD38 found at low levels on RBCs and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh (Rhesus factor) blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. RBC genotyping is not impacted by daratumumab and may be performed at any time.

The initial release of cytokines associated with the start of teclistamab and talquetamab treatment could suppress CYPs. The highest risk of interaction is expected to be from initiation of teclistamab and talquetamab step-up schedule up to 7 days after the first maintenance dose or during a CRS event.

During this time period, toxicity or medicinal product concentrations (e.g., cyclosporin) should be monitored in patients who are receiving concomitant CYP substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

31.9.2. Management of CRS and ICANs (relevant to both teclistamab and talquetamab)

Cytokine release syndrome (CRS):
CRS, including life-threatening or fatal reactions, may occur in patients receiving teclistamab and talquetamab.

Clinical signs and symptoms of CRS may include but are not limited to fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, adult respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation.

Treatment should be initiated with teclistamab and talquetamab according to the step-up dosing schedule to reduce risk of CRS. Pre-treatment medicinal products (corticosteroids, antihistamine and antipyretics) should be administered prior to each dose of the teclistamab and talquetamab step-up dosing schedules, to reduce risk of CRS.

Management of CRS is shown below as per the SPCs for these agents. Local variations for the management of CRS can be followed for patients managed via an ambulatory care pathway or in accordance with local practice. The use of prophylactic tocilizumab is permitted if this is part of local protocols. Tocilizumab will not be reimbursed.

CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension.

If CRS is suspected, teclistamab and talquetamab should be withheld until the adverse reaction resolves (see Table 15 and Table 17, respectively). CRS should be managed according to the recommendations below. Supportive care for CRS (including but not limited to anti-pyretic agents, IV fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation, haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.

Table 19: Recommendations for management of CRS with tocilizumab and corticosteroids

Grade[e]	Presenting symptoms	Tocilizumab[a]	Corticosteroids[b]
Grade 1	Temperature ≥ 38°C[c]	May be considered.	Not applicable.
Grade 2	Temperature ≥ 38°C[c] with either: • Hypotension responsive to fluids and not requiring vasopressors, or • Oxygen requirement of low-flow nasal cannulad or blow-by	Administer tocilizumab[b] 8mg/kg intravenously over 1 hour (not to exceed 800mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period;	If no improvement within 24 hours of starting tocilizumab, administer methylprednisolone 1mg/kg intravenously twice daily, or dexamethasone 10mg intravenously every 6 hours. Continue corticosteroid use until the event is grade 1 or less, then taper over 3 days.

		maximum total of 4 doses.	
Grade 3	Temperature ≥ 38°C[c] with either: • Hypotension requiring one vasopressor with or without vasopressin, or • Oxygen requirement of high-flow nasal cannulad, facemask, non-rebreather mask, or Venturi mask	Administer tocilizumab 8mg/kg intravenously over 1 hour (not to exceed 800mg). Repeat tocilizumab every 8 hours as needed, if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	If no improvement, administer methylprednisolone 1mg/kg intravenously twice daily, or dexamethasone 10mg intravenously every 6 hours. Continue corticosteroid use until the event is grade 1 or less, then taper over 3 days.
Grade 4	Temperature ≥ 38°C[c] with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	Administer tocilizumab 8mg/kg intravenously over 1 hour (not to exceed 800mg). Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24-hour period; maximum total of 4 doses.	As above, or administer methylprednisolone 1000mg intravenously per day for 3 days, per physician discretion. If no improvement or if condition worsens, consider alternate immunosuppressants[b].
[a] Refer to tocilizumab prescribing information for details. [b] Treat unresponsive CRS per institutional guidelines. [c] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy (e.g., tocilizumab or corticosteroids). [d] Low-flow nasal cannula is ≤ 6 L/min, and high-flow nasal cannula is >6 L/min. [e] Based on ASTCT grading for CRS (Lee et al 2019).			

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS):

Serious or life-threatening neurologic toxicities, including ICANS occurred following treatment with teclistamab and talquetamab.

Patients should be monitored for signs or symptoms of neurologic toxicities during treatment and treated promptly.

Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur. At the first sign of neurologic toxicity, including ICANS, patients should be immediately evaluated and treated based on severity. Patients who experience grade 2 or higher ICANS or first occurrence of grade 3 ICANS with the previous dose of teclistamab and talquetamab should be instructed to remain within proximity of a healthcare facility and monitored for signs and symptoms daily for 48 hours.

For ICANS and other neurologic toxicities, treatment with teclistamab and talquetamab should be withheld as indicated in Table 15 and Table 17, respectively.

Due to the potential for ICANS, patients should be advised not to drive or operate heavy machinery during the teclistamab and talquetamab step-up dosing schedule and for 48 hours after completing the step-up dosing schedule and in the event of new onset of any neurological symptoms.

Management of neurologic toxicities:

At the first sign of neurologic toxicity, including ICANS, neurology evaluation should be considered. Other causes of neurologic symptoms should be ruled out. Teclistamab and talquetamab should be withheld until adverse reaction resolves (see Table 15 and Table 17). Intensive care and supportive therapy should be provided for severe or life-threatening neurologic toxicities. General management for neurologic toxicity (e.g., ICANS with or without concurrent CRS) is summarised below:

Table 20: Recommendations for management of ICANS

<table>
<tr><th>Grade</th><th>Presenting symptoms[a]</th><th>Concurrent CRS</th><th>No Concurrent CRS</th></tr>
<tr><td rowspan="2">Grade 1</td><td rowspan="2">ICE score 7-9[b]

Or, depressed level of consciousness[c]: awakens spontaneously.</td><td>Management of CRS per Table 19.

Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td><td>Monitor neurologic symptoms and consider neurology consultation and evaluation, per physician discretion.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis.</td></tr>
<tr><td rowspan="2">Grade 2</td><td rowspan="2">ICE score 3-6[b]

Or, depressed level of consciousness[c]: awakens to voice.</td><td>Administer tocilizumab per Table 19 for management of CRS.

If no improvement after starting tocilizumab, administer dexamethasone[d] 10mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until resolution to grade 1 or less, then taper.</td><td>Administer dexamethasone[d] 10mg intravenously every 6 hours.

Continue dexamethasone use until resolution to grade 1 or less, then taper.</td></tr>
<tr><td colspan="2">Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.</td></tr>
<tr><td>Grade 3</td><td>ICE score 0-2[b]

Or, depressed level of consciousness[c]: awakens only to tactile stimulus, or

seizures[c], either:
• any clinical seizure, focal or generalised</td><td>Administer tocilizumab per Table 19 for management of CRS.

In addition, administer dexamethasone[d] 10mg intravenously with the first dose of tocilizumab, and repeat dose every 6 hours. Continue dexamethasone use until</td><td>Administer dexamethasone[d] 10mg intravenously every 6 hours.

Continue dexamethasone use until resolution to grade 1 or less, then taper.</td></tr>
</table>

	that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local oedema on neuroimaging[c].	resolution to grade 1 or less, then taper.	
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed.	
Grade 4	ICE score 0[b] Or, depressed level of consciousnessc either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[c], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[c]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure / cerebral oedemac, with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • cushing's triad.	Administer tocilizumab per Table 19 for management of CRS. As above, or consider administration of methylprednisolone 1000mg per day intravenously with first dose of tocilizumab, and continue methylprednisolone 1000mg per day intravenously for 2 or more days.	As above, or consider administration of methylprednisolone 1000mg per day intravenously for 3 days; if improves, then manage as above.
		Consider non-sedating, anti-seizure medicinal products (e.g., levetiracetam) for seizure prophylaxis. Consider neurology consultation and other specialists for further evaluation, as needed. In case of raised intracranial pressure/cerebral oedema, refer to institutional guidelines for management.	

[a] Management is determined by the most severe event, not attributable to any other cause.
[b] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., " show me 2

fingers" or " close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (grade 4 ICANS) = 0 points.
[c] Attributable to no other cause.
[d] All references to dexamethasone administration are dexamethasone or equivalent.

In addition to ICANS, talquetamab has additionally been associated with cerebellar adverse events. These should be monitored for and talquetamab held at first sign of onset.

31.10. Concomitant medication and monitoring for daratumumab, teclistamab and talquetamab

31.10.1. Dara-Tec and Dara-Tal

Further concomitant medication and monitoring for talquetamab only is provided in Section 31.10.2.

Blood products and growth factors (e.g., GCSF, EPO) are encouraged to support blood counts where necessary.

Bone directed therapy as per 19.12.1.

CYP450 substrates with narrow therapeutic index should be used with caution from the start of step-up doses up to 7 days after the first treatment dose of or talquetamab are administered, as well as during any event of CRS.

Use of warfarin (or other vitamin K antagonists) during Cycle 1 should be avoided unless no other therapeutic option is available. For participants who cannot switch to a different anticoagulant and who experience CRS, coagulation parameters should be monitored closely during a CRS event and until CRS symptoms resolve.

The use of transdermal patches at the injection site should be avoided.

Complementary therapies including St Johns Wort and their interactions have not been fully studied for all IMPs and therefore should be avoided unless individually reviewed by local pharmacy and the treating physician.

Infections:
Severe, life-threatening, or fatal infections have been reported in patients receiving daratumumab, teclistamab, and talquetamab. New or reactivated viral infections have also occurred during therapy with daratumumab, teclistamab and talquetamab.

Patients should be monitored for signs and symptoms of infection prior to and during treatment with daratumumab, teclistamab, and talquetamab and treated appropriately. Prophylactic antimicrobials should be administered according to local institutional guidelines.

Recommended infection prophylaxis (local policies providing a similar spectrum of protection can be followed if different to the below):

- Aciclovir 400mg twice daily,
- Co-trimoxazole 480mg twice daily on Mon/Wed/Fri,
- Fluconazole 50mg once daily, and
- Additional antibiotic prophylaxis, e.g., levofloxacin, azithromycin, in the event of neutropenia or recurrent infections.

Hypogammaglobulinaemia has been reported particularly in patients receiving teclistamab and talquetamab and associated with an increased risk of infections. **IgG levels should be monitored during treatment with teclistamab and talquetamab and replacement immunoglobulins (SC or IV) should be instituted according to local guidelines and committee recommendations.**

Hepatitis B virus reactivation can occur in patients treated with all medicinal products directed against B cells, and in some cases, may result in fulminant hepatitis, hepatic failure, and death.

Patients with evidence of positive HBV serology indicative of past infection should be managed in consultation with hepatology and receive prophylaxis against reactivation as indicated. Whether receiving prophylaxis or not patients should be monitored for clinical and laboratory signs of HBV reactivation while receiving teclistamab, and for at least six months following the end of teclistamab treatment.

In patients who develop reactivation of HBV, daratumumab, teclistamab, and talquetamab should be withheld and HBV managed per local institutional guidelines.

Reactivation of other viruses including cytomegalovirus, adenovirus, and EBV has been identified, particularly with anti-BCMA bispecific antibodies. If not routinely monitored for, these infections should be tested for at the first signs of suggestive symptoms and treated accordingly.

Progressive Multifocal Leukoencephalopathy from reactivation of John Cunningham virus, which can be fatal, has also been reported in patients receiving daratumumab and teclistamab. Patients should be monitored for any new onset of, or changes in, pre-existing neurological signs or symptoms. If PML is suspected, treatment with daratumumab, teclistamab and talquetamab should be withheld and appropriate diagnostic testing initiated. If PML is confirmed, daratumumab, teclistamab, and talquetamab must be discontinued.

Vaccines:
Immune response to vaccines may be reduced when taking daratumumab, teclistamab and talquetamab but vaccination as per NHS standard of care, with non-live vaccines, should be encouraged. This should include COVID-19, flu, pneumococcal and RSV for those eligible.

31.10.2. Talquetamab-specific

Oral toxicity:
Oral toxicities, including dysgeusia, dry mouth, dysphagia, and stomatitis occur very commonly following treatment with talquetamab.

Patients should be monitored for signs and symptoms of oral toxicity. Patients should be counselled to seek medical attention should signs or symptoms of oral toxicity occur, and supportive care should be provided. Supportive care may include saliva stimulating agents, steroid mouth wash, or consultation with a nutritionist. Talquetamab should be interrupted or less frequent dosing should be considered as per Table 17.

Over time, notable weight loss may occur. Weight change should be monitored regularly during therapy. Clinically significant weight loss should be further evaluated. Talquetamab should be interrupted or less frequent dosing should be considered as per Table 17.

Skin reactions:
Talquetamab can cause skin reactions including rash, maculo-papular rash, erythema, erythematous rash, as well as nail disorders. Skin reactions including rash progression should be monitored for early intervention and treatment with corticosteroids. For grade 3 or higher, or worsening grade 1 or 2 rashes,

oral steroids should also be administered. For non-rash skin reactions dose modification may be considered as per Table 17.

For skin reactions and nail disorders, talquetamab should be withheld based on severity and institutional guidelines should be followed.

31.10.3. Prohibited con-medications for daratumumab, teclistamab, and talquetamab

1. Any treatment for myeloma, including participation in any other interventional study for myeloma that involves an IMP, is prohibited, except the following:
   d. Local radiotherapy to relieve bone pain, spinal cord compression or directed at an anatomically threatening lesion,
   e. Bisphosphonate or other bone-directed treatment, or
   f. Systemic corticosteroids for myeloma treatment as specified in the protocol (see Section 29) (steroid treatment delivered by any route for other co-morbid conditions is allowed when considered necessary by the treating physician).
2. Live vaccinations are contra-indicated.

31.11. Trial restrictions for daratumumab, teclistamab, and talquetamab

The effects of daratumumab, teclistamab and talquetamab during pregnancy are unknown. Female participants should avoid becoming pregnant and male participants should avoid impregnating a female partner, as outlined in Appendix 48.10. Daratumumab, teclistamab, and talquetamab should be prescribed as outlined within this protocol and the trial-supplied SmPC.

31.11.1. Pregnancy testing, fertility and contraception for daratumumab, teclistamab and talquetamab

Human IgG is known to cross the placenta after the first trimester of pregnancy. Therefore, teclistamab and talquetamab, humanised IgG4-based antibodies and daratumumab, human IgG1κ antibody, have the potential to be transmitted from the mother to the developing foetus.

There are no available data on the use of teclistamab or talquetamab in pregnant women or animal data to assess the risk of their use in pregnancy. There are no or limited amount of data from the use of daratumumab in pregnant women.

There are no data on the effect of daratumumab, teclistamab and talquetamab on fertility in males or females.

Therefore, the following precautions should be followed:

- Pregnancy status for women of child-bearing potential should be verified prior to starting treatment with daratumumab, teclistamab and talquetamab,
- Women of child-bearing potential should use effective contraception during treatment and for three months after the final dose of daratumumab and talquetamab and five months after the final dose of teclistamab (whichever is longer), and
- Male patients with a female partner of child-bearing potential should use effective contraception during treatment and for three months after the last dose of teclistamab.

32. iFIT1 STATISTICS AND DATA ANALYSIS

32.1. iFIT1 Sample size calculation

Data from MAIA showed that 90% of MRD positive patients were alive and progression-free at 6 months and 65% were alive and progression-free at 30 months [12]. This equates to 72% of those patients who were MRD positive and alive and progression-free at 6 months remaining alive and progression-free at 30 months.

The minimal clinically important difference for TCE use in this setting is an increase of 10% in the proportion of patients alive and progression-free after 24 months of maintenance therapy. There is currently no randomised PFS data for TCE use in this population. However, data from MajesTEC-1 showed the ability of TCE to prolong deep responses in patients after multiple prior lines of therapy [79].

An increase of 10% in the proportion of patients alive and progression-free after 2-years of maintenance therapy, assuming 4 years of recruitment, 2 years of follow-up, 80% power and a two-sided significance level of 2.5% requires 585 patients (195:195:195) with 158 events per comparison. The 10% increase at 2-years equates to a hazard ratio of 0.60.

The significance level of 2.5% is used to account for the multiple testing across the three arms using the Bonferroni approach [92]. This has been chosen to control the multiple superior false positive rate (rejecting both null hypotheses incorrectly) at 0.176% and the family wise error rate (rejecting at least one null hypothesis incorrectly) at 4.65% [93].

If both TCE arms should prove superior to the standard treatment arm, then the secondary safety and QoL endpoints will be used to compare between them. These will be non-powered comparisons. Of particular interest is the incidence of grade 3, 4, and 5 infections, which have contributed to 24.5% [94] of reported adverse events (AEs) in single-agent bispecific antibody trials [94].

32.2. Statistical analysis

32.2.1. General considerations

A full SAP will be written for **iFIT1** before any analyses are undertaken. Refer to Section 21.3.1 for further details of the general considerations regarding the **iFIT1** statistical analysis.

All analyses will be conducted using the ITT population for **iFIT1**. This population will include participants according to their randomised treatment allocation, regardless of eligibility, whether they prematurely discontinued treatment, or did not comply with the treatment regimen.

If there are a considerable number of protocol violators in **iFIT1**, a per-protocol (PP) analysis will be considered for the primary endpoint. The PP population will exclude participants who do not receive their randomly allocated treatment or who are found to have breached key eligibility criteria, as defined in the **iFIT1** SAP, following randomisation.

The safety population for **iFIT1** will consist of all participants who received at least one dose of study treatment, according to the treatment received rather than randomised treatment allocation.

32.2.2. Frequency of analysis

Interim statistical summaries will be presented to the DMEC in strict confidence at approximately yearly intervals as described in the DMEC charter.

A formal interim analysis for **iFIT1** will be conducted when half of the required events (79 per comparison) have been observed, estimated to be 3 months following the end of recruitment. This will be conducted at the 0.001 significance level using the Haybittle-Peto approach [95].

The DMEC, in the light of the interim data, and any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that a treatment is better and recommend appropriate changes to the trial protocol.

No other formal interim analyses are planned in **iFIT1** before the participants have attained the primary endpoint, which will be triggered by the required number of events (158 per comparison). It is assumed that this will be 2 years following the end of recruitment. Analysis of other endpoints and secondary comparisons will be undertaken alongside this analysis, as appropriate.

32.2.3. Summary of baseline data and flow of patients

The CONSORT [71] flow diagram will be used to summarise the course of participants through the study. Summary tables will show the number of participants in each analysis population by **iFIT1** randomised treatment allocation. Summaries of protocol violations/deviations, including breaches of eligibility criteria and the reasons for non-registrations, non-randomisations, withdrawals, and permanent discontinuation of treatment will also be presented. Additionally, summaries of follow-up time from registration and randomisation will be presented overall and by arm for **iFIT1**.

The characteristics of those randomised into **iFIT1** will be tabulated and appropriately summarised. Each summary will be presented overall and by randomised treatment allocation and will include the information collected on the baseline eCRFs, including, but not limited to:

- Stratification factors used for **iFIT1** randomisation,
- Age (years) at registration,
- Sex,
- Ethnicity,
- IMD,
- ECOG performance status at registration and **iFIT1** baseline,
- Karnofsky performance status at registration and **iFIT1** baseline,
- Paraprotein type,
- Light chain type,
- Immunoglobulin status at registration and **iFIT1** baseline,
- Cytogenetic risk status at registration,
- ISS at registration and **iFIT1** baseline (see Appendix 48.8),
- R-ISS at registration and **iFIT1** baseline (see Appendix 48.8),
- R2-ISS at registration and **iFIT1** baseline (see Appendix 48.8),
- IMWG frailty category at registration and **iFIT1** baseline (see Appendix 48.3), and
- UK-MRA MRP category at registration and **iFIT1** baseline (see Appendix 48.9).

For **iFIT1**, the post-DRd induction therapy response will also be tabulated. Categorical outcomes will be presented as numbers and percentages, using the total number of forms expected as the denominator; presentation of continuous outcomes will include means, standard deviations, medians, interquartile ranges, and ranges. Missing or unobtainable data will be included as missing in these summaries unless data are available from the 24-hour randomisation system. No statistical testing will be carried out when summarising these data.

32.2.4. Primary endpoint analysis

Survival curves stratified by randomised treatment allocation, plotting the time since **iFIT1** randomisation against the proportion of participants alive and progression-free, and the corresponding 95% confidence intervals will be estimated using the Kaplan-Meier approach. The median PFS times and 95% confidence intervals, overall and by randomised treatment allocation, will be estimated from these plots. The percentages of those alive and progression-free at yearly intervals following **iFIT1** randomisation will also be estimated overall and by randomised treatment allocation along with 95% confidence intervals.

PFS in **iFIT1** will be assessed using Cox proportional hazards regression, adjusting for the stratification factors used in the **iFIT1** randomisation. DRd maintenance to progression will be used as the reference level such that a treatment effect coefficient less than one equates to a reduction in the hazard of death or progression in the experimental arm. There will be no pairwise comparison between the TCE arms. A statistically significant treatment effect will be suggested if the p-value for the corresponding hazard ratio is <0.025. Parameter estimates, hazard ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model.

The proportional hazards assumptions will be assessed by plotting the hazards over time (i.e., the log cumulative hazards plot) for each treatment arm and using appropriate statistical tests. If evidence is found to support the violation of the proportional hazards assumption, then alternative appropriate analysis methods will be investigated.

32.2.5. Secondary endpoint analysis

OS and other time-to-event endpoints will be analysed using methods similar to those described for the primary endpoint.

For both the ORR and maximum response endpoints, the number and proportion of participants in each response category (sCR, CR, VGPR, etc.) will be summarised by randomised treatment allocation and exact 95% confidence intervals will be calculated. The difference in proportions for each response category will be presented with corresponding 95% confidence intervals.

For attainment of ≥VGPR, and other binary endpoints, the number and proportion of participants will be summarised by randomised treatment allocation and exact 95% confidence intervals will be calculated. A logistic regression model will regress the endpoint on randomised treatment allocation, adjusting for the stratification factors used in the **iFIT1** randomisation. Parameter estimates, odds ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model. Residuals and predicted values produced from the models will be examined to assess the assumptions of the statistical models.

Adverse events will be summarised using NCI-CTCAE V5.

Cumulative incidence function curves, plotting time since **iFIT1** randomisation against cumulative incidence of SPMs, overall and stratified by randomised treatment allocation will be estimated along with 95% confidence intervals. Deaths not resulting from SPMs will be considered unrelated for this analysis, and participants affected will be censored at the date of death.

The incidence, type, and grades of infections along with any prophylactic treatment given within **iFIT1** will be summarised descriptively. These will be summarised by randomised treatment allocation where appropriate. The rate of infections between the experimental and control arms will be analysed using an Anderson-Gill model for recurrent events.

QoL will be summarised using mean scores and 95% CIs for each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role, and functioning domain, for each EORTC QLQ-IL413 infection symptom scale item and domain, and for each EORTC QLQ-IL414 item and domain, at each assessment timepoint. Similar descriptive summaries will be produced for QALYs, as scored by the EQ-5D-5L questionnaire. Modelling will be conducted to account for the longitudinal nature of the data and the stratification factors, as well as the baseline QoL measurement (end of DRd induction). This, and procedures for missing data, will be detailed in the QoL SAP.

32.2.6. Exploratory endpoint analysis

The methods for analysis of exploratory endpoints will be detailed within the separate **iFIT1** SAP.

Subgroup analysis will be conducted to determine whether a selection of genetic characteristics and medical history are prognostic of the incidence of infection.

A risk prediction model for infections will be developed and reported following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis and Artificial Intelligence (TRIPOD+AI) guidelines [96].

32.2.7. Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology/serological results, biochemistry results, and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the following endpoints: PFS, PFS2, OS, attainment of ≥VGPR and attainment of MRD negativity. Note that for the attainment of ≥VGPR and attainment of MRD negativity endpoints, only response subgroups defined before the endpoint timepoint will be analysed. The subgroup analysis of each endpoint will follow the same structure as the main analysis of the respective endpoint where appropriate interaction terms will be added to the regression models to account for the subgroup being investigated.

<u>Patient Characteristics:</u>

- Age (years) at registration (<70, 70 to 80, >80),
- Sex (male, female),
- Ethnicity (White, Mixed, Asian, Black, other, prefer not to say, missing),
- IMD (first, second, third, fourth quartile, missing),
- ECOG performance status at registration (0, 1, ≥2, missing),
- Karnofsky performance status at registration (<80, 80 to 90, >90, missing),
- IMWG frailty category at registration and **iFIT1** baseline (FIT, UNFIT; see Appendix 48.3),
- ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R-ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R2-ISS at registration (Stage I, Stage II, Stage III, Stage IV, missing; see Appendix 48.8), and
- UK-MRA MRP category at registration and **iFIT1** baseline (low, medium, high, missing; see Appendix 48.9).

<u>Haematology/Serological Results:</u>

- Haemoglobin concentration at registration (<100, ≥100g/L),
- White blood cells at registration (<LLN (lower limit of normal), ≥LLN),
- Neutrophil count at registration (<LLN, ≥LLN),
- Lymphocyte count at registration (<LLN, ≥LLN),
- Platelets at registration (<150, ≥150 x 10^9/L), and
- Plasma cells in bone marrow at registration (<60%, ≥60%).

Biochemistry Results:

- β_2M concentration at registration (< 3.5, 3.5 to <5.5, ≥5.5mg/L, missing),
- Serum creatinine concentration at registration (<175, ≥175µmol/L, missing),
- Corrected serum calcium concentration at registration (<2.75, ≥2.75mmol/L, missing),
- Serum albumin at registration (<ULN, ≥ULN, missing),
- LDH at registration (<ULN, ≥ULN, missing),
- CRP at registration (<ULN, ≥ULN, missing),
- Total bilirubin* at registration (<ULN, ≥ULN, missing), and
- ALT/AST at registration (<ULN, ≥ULN, missing).

*Except in participants with congenital bilirubinaemia (Gilbert's Syndrome), in which case direct bilirubin will be used.

Cytogenetic/Molecular Results:

- t(4,14) at registration (detected, not detected, not tested),
- t(14,16) at registration (detected, not detected, not tested),
- t(14,20) at registration (detected, not detected, not tested),
- del(17p) at registration (detected, not detected, not tested),
- del(13q) at registration (detected, not detected, not tested),
- del(1p) at registration (detected, not detected, not tested),
- gain(1q) at registration (detected, not detected, not tested),
- Hyperdiploidy at registration (detected, not detected, not tested),
- TP53 mutation status (detected, not detected, not tested),
- IMWG definition risk group at registration (high risk, standard risk, missing), and
- UK definition risk group at registration (ultra-high risk, high risk, standard risk, missing).

Response:

- Response to DRd induction (<VGPR, ≥VGPR),
- Response to **iFIT1** treatment at 18 cycles of treatment (<VGPR, ≥VGPR),
- Response to **iFIT1** treatment at either 30 cycles of treatment, or 18 cycles of treatment and 12 cycles of active monitoring, as appropriate (<VGPR, ≥VGPR),
- MRD response to DRd induction (positive, negative, unable to determine),
- MRD response to **iFIT1** treatment at 18 cycles of treatment (positive, negative, missing), and
- MRD response to **iFIT1** treatment at either 30 cycles of treatment, or 18 cycles of treatment and 12 cycles of active monitoring, as appropriate (positive, negative, missing).

Further subgroup analyses may be undertaken, as appropriate and all subgroup analysis will be fully documented in the separate **iFIT1** SAP.

Subgroup analyses may, by chance, generate false negative or positive results. Those carried out will be interpreted with caution.

V. iFIT2 RANDOMISATION PATHWAY

33. iFIT2 BACKGROUND AND RATIONALE

iFIT2 - addressing whether ongoing dexamethasone therapy is needed for FRAIL patients with a suboptimal response to induction therapy

For frail patients, even if their disease remains MRD positive after induction, a less-intense approach to ongoing treatment is preferred due to the toxicity risks with TCE therapy outlined above. Based on the findings of the Italian study [97] which showed no benefit from continuing dexamethasone alongside lenalidomide in the UNFIT patient group we propose to ask a similar question but with DRd compared to DR in the FRAIL population. DR is being compared to Rd in FRAIL patients in the IFM2017-03 study [98] but there has been no comparison to DRd to date. Dexamethasone has significant side effects, driven by metabolic alteration, which include mood and sleep disturbance, blurred vision, peripheral oedema and cognition changes which may particularly affect the oldest, frailest patients. Therefore, we plan to test whether dexamethasone can be removed from treatment, offering a more patient-centric treatment with a focus on reducing toxicity but potentially also improving their tolerance of the DR combination, minimising dose reductions and discontinuations and improving their outcomes. This pathway addresses the James Lind Alliance priority "How can we safely reduce, cycle, or stop the use of medications to reduce the side effects of treatment and maintain control over myeloma".

34. iFIT2 OBJECTIVES AND ENDPOINTS

34.1. iFIT2 Primary objectives

To determine the impact on EFS when switching from DRd maintenance therapy to progression to DR maintenance therapy to progression, in patients who are MRD positive and FRAIL by IMWG frailty assessment after six cycles of DRd induction therapy.

The alternative hypothesis is that DR maintenance therapy will result in a difference in EFS at 24 months post-randomisation, compared to DRd maintenance therapy to progression. Superiority of DR maintenance therapy is anticipated. The null hypothesis is that there is no difference in EFS at 24 months post-randomisation.

34.2. iFIT2 Secondary objectives

The secondary objectives are to assess the impact of switching from DRd maintenance therapy to progression to DR maintenance therapy to progression, in patients who are MRD positive and FRAIL by IMWG frailty assessment after six cycles of DRd induction therapy, on the following endpoints:

1. Progression-free survival (PFS),
2. Time to progression (TTP),
3. Time to second PFS event (PFS2),
4. Overall survival (OS),
5. Overall response rate (ORR),
6. Attainment of ≥VGPR,
7. Maximum response,
8. Time to improved response,
9. Treatment compliance,
10. Toxicity and safety,
11. Incidence of secondary primary malignancies (SPMs),
12. Incidence, rate, and type of infections,
13. Quality of life (QoL), and
14. Cost-utility.

34.3. iFIT2 Exploratory objectives

There are no exploratory objectives currently defined for **iFIT2**.

34.4. iFIT2 Endpoints

Response to treatment, including progression, will be defined using the IMWG response criteria [91] (see Appendix 48.2) for all relevant endpoints.

34.4.1. iFIT2 Primary endpoint

Event-free survival (EFS)
The time from **iFIT2** randomisation to the first of the following events: grade 4 haematological AEs (anaemia, neutropenia, thrombocytopenia), grade 3 and 4 non-haematological AEs (including SPMs), discontinuation of trial treatment, progression [91] or death. Participants event-free at the time of analysis will be censored at their last date known to be alive and event-free.

34.4.2. iFIT2 Secondary endpoints

Progression-free survival (PFS)
The time from **iFIT2** randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Time to progression (TTP)
The time from **iFIT2** randomisation to first documented evidence of disease progression. Participants who die without disease progression will be censored at their date of death. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Time to second PFS event (PFS2)
The time from **iFIT2** randomisation to the second documented evidence of disease progression or death from any cause. Participants alive and for whom a second progression has not been observed at the time of analysis will be censored at their last known date to be alive and second progression-free.

Overall survival (OS)
The time from **iFIT2** randomisation to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive.

Overall response rate (ORR)
The categorical response to treatment at the end of cycle 6 of **iFIT2** treatment: sCR, CR, VGPR, PR, MR, SD, or PD.

Attainment of ≥VGPR
The binary response to treatment at the end of cycle 6 of **iFIT2** treatment when OS is dichotomised as ≥VGPR (sCR, CR, VGPR) versus <VGPR (PR, MR, SD, PD).

Maximum response
The maximum response attained at any point after **iFIT2** randomisation.

Time to improved response
The time from **iFIT2** randomisation to first recorded improved response, where the baseline response is that recorded at the start of randomised treatment (**iFIT2** cycle 1, day 1). Participants whose disease progresses or who die before an improved response is recorded will be censored at the time of

progression or death, respectively. Participants alive with no improved response recorded at the time of analysis will be censored at their last known date to be alive.

Treatment compliance
Compliance with **iFIT2** treatment will be assessed in multiple ways: a binary variable indicating whether all cycles of treatment were completed, the number of cycles completed, and the total dose of each trial medication received. The number and causes of dose omissions, dose delays, and dose reductions will also be reported, by trial medicinal product.

Toxicity and safety
All AEs, ARs, SAEs, SARs, and SUSARs reported following **iFIT2** randomisation, as graded by NCI-CTCAE V5. Also included are the numbers of pregnancies in both trial participants and their partners where appropriate.

Incidence of secondary primary malignancies (SPMs)
The number and details of all other cancers, defined as SPMs, reported following **iFIT2** randomisation.

Incidence, rate, and type of infections
In the first instance, this is defined as the proportion of participants in the **iFIT2** pathway experiencing an infection of any type or grade, as graded by NCI-CTCAE V5. Rate of infection is the number of infections experienced divided by the total number of participant days in the **iFIT2** pathway. This will then be extended to consider grade 3, 4, and 5 infections only and then each type of infection (e.g., fungal, viral, bacterial) separately.

Quality of life (QoL)
Health-related QoL, as scored using the following participant reported questionnaires: EQ-5D-5L, EORTC QLQ-C30 and QLQ-MY20. Participant-reported infections will be assessed using the EORTC QLQ-IL413. QoL questionnaires will be completed at 3, 6, 12, 18, 24, and 30 months post-**iFIT2** randomisation. End of DRd induction is defined as the baseline QoL for **iFIT2**.

Cost-utility
ICERs indicating cost per QALY will be the primary economic evaluation endpoint. Costs will include therapy and healthcare resource use costs. QALYs will be estimated using survival, adjusted for quality according to the EQ-5D-5L. Probability of cost-effectiveness and net health benefit estimates will also be presented. Willingness to pay for QALY gained will assumed to be in the range £20,000-£30,000 as per NICE guidance.

34.4.3. iFIT2 Exploratory endpoints

There are no exploratory endpoints currently defined for **iFIT2**.

35. iFIT2 TRIAL DESIGN

iFIT2 will assess whether dropping dexamethasone and continuing DR only to progression improves EFS compared to continuing DRd to progression in patients who are MRD positive and FRAIL. Eligible participants will be randomly allocated, using a minimisation algorithm with a random element, in a 1:1 ratio to receive DRd to progression (standard care), or DR to progression. A total of 279 participants are required to be randomised in order to reach the sample size for the powered comparison.

36. iFIT2 PARTICIPANT ELIGIBILITY

Eligibility waivers to inclusion/exclusion criteria are not permitted.

Confirmation of eligibility for the **iFIT2** pathway must be recorded in the patient's notes. If a participant is not eligible for their assigned **iFIT2** pathway, they cannot continue in the trial at all, i.e., not under any pathway.

36.1. Trial randomisation – iFIT2 pathway

Participants must meet all of the following inclusion criteria and none of the exclusion criteria.

Each participant must only be randomised once.

36.1.1. Inclusion criteria for iFIT2

1. Completed 6 cycles of DRd induction therapy after registering within the iFIT study,
2. Planned to continue on all three DRd medications (dose reductions are allowed),
3. Achieved a partial response (PR) biochemically (irrespective of MRD status), or achieved a ≥VGPR and are MRD positive, as confirmed by HMDS,
4. Categorised as FRAIL according to the IMWG frailty index (see Appendix 48.3),
5. Able to provide full informed consent, and
6. Prepared to comply with pregnancy prevention plan.

36.1.2. Exclusion criteria for iFIT2

1. Received systemic anti-myeloma therapy other than daratumumab, lenalidomide and dexamethasone prior to randomisation. Steroids given (by any route) for reasons other than myeloma disease control are allowed,
2. Received a stem cell transplant,
3. Stable disease (SD) or progressive disease (PD) as per IMWG response criteria (see Appendix 48.2),
4. Pregnant, breast feeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within 3 months after the last dose, or
5. Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring.

37. iFIT2 TRIAL PROCEDURES

The following section should be consulted in line with Section 18.

37.1. Non-randomisation

For participants who do not undergo **iFIT2** randomisation, the reason should be recorded on the applicable eCRF.

Reasons for non-randomisation will be monitored by the CTRU alongside recruitment progress.

37.2. iFIT2 trial randomisation system

iFIT2 randomisation will be performed using the CTRU automated 24-hour web-based system. An authorised PIN will be required for first time users to access the system. They will be provided by the CTRU to staff approved to use the system by the PI on the trial APL, after the research site has received formal approval to open to recruitment. Existing users will access the system using their email and personal password. All registrations and randomisations can be accessed using the following link: https://lictr.leeds.ac.uk/webrand/.

Care must be taken to ensure the correct "randomisation pathway" (**iFIT2**) , site code and trial ID are selected/entered to ensure correct randomisation into **iFIT2**.

37.3. iFIT2 randomisation

37.3.1. Consent for iFIT2 randomisation

Once it is known that the participant will be assigned to the **iFIT2** randomisation pathway (expected to be *around* standard of care induction cycle 6 day 28), the potential participant will be provided with a full verbal explanation of the **iFIT2** treatment pathway and be given the **iFIT2** PISICD to consider. It is the responsibility of the research site to ensure that the participant still has a copy of the Study Registration PIS and Additional Information PIS to refer to. Following information provision, participants will be given the opportunity to further discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to continue their participation in the trial. The right of a participant to refuse to continue their participation in the trial without giving reasons must be respected.

Participants wishing to continue their participation in their assigned **iFIT2** pathway will be required to provide full informed consent using the **iFIT2** ICD.

37.3.2. Eligibility and assessments prior to iFIT2 randomisation

Upon completion of 6 cycles of standard of care induction, after confirmation from CTRU re randomisation pathway assignment, and within 14 days prior to **iFIT2** randomisation, the following local investigations and assessments must be performed to confirm eligibility for randomisation. Note that if randomisation does not occur within 14 days of the assessments following the end of standard of care induction, then repeat assessments will be required to confirm eligibility (except central bone marrow samples and translational blood sample).

There must be no break in treatment of more than 6 weeks from cycle 6 day 28 of standard of care induction. If treatment is delayed after cycle 6 day 28 for 6 weeks or more, the participant will be considered as off-trial unless discussed and agreed with the CIs, after which point further treatment will be at the discretion of the treating clinician.

Local investigations prior to randomisation

- Review of medical history in line with eligibility criteria for **iFIT2,**
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine, and
- Calculated CrCl (CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospital is not accurate is older patients).

37.3.3. iFIT2 randomisation

Full informed consent for continuation in the trial in the **iFIT2** pathway must be obtained prior to randomisation.

Once participants have given full informed consent and are confirmed eligible, they can be randomised. The participant will continue to use the same trial number as allocated to them at registration.

The following information will be required at randomisation:

- Name of person performing the randomisation,
- Research site name and site code,
- Trial ID number (as allocated at registration),
- Participant details, including initials, date of birth and NHS/CHI number,
- Confirmation of eligibility,
- Confirmation of full informed consent, and
- Email address and/or phone number of participants who choose to complete questionnaires online.

Care must be taken to ensure the correct "randomisation pathway" (iFIT2) , site code and trial ID are selected/entered to ensure correct randomisation into iFIT2.

24-hour iFIT2 randomisation:

https://lictr.leeds.ac.uk/webrand/

Following randomisation, completed **iFIT2** consent forms must be sent via the CTRU Secure File Transfer Service or other CTRU-approved method (never standard e-mail).

Automated confirmation of **iFIT2** randomisation will be emailed to the research site team. The local hospital will provide each participant with a trial ID card, which they should carry with them at all times and present to medical staff should they be admitted to hospital during their time on the trial. Eligibility for **iFIT2** treatment must be confirmed on the applicable eCRF before **iFIT2** treatment can start.

The research site team should notify the participant's GP that they are continuing to take part in the trial under the **iFIT2** pathway using the approved template letter provided by the CTRU. A copy of the letter should be filed in the ISF.

Participants will be randomly allocated on a 1:1 basis to receive either:

- Continue DRd therapy until PD, or
- DR (no dexamethasone) therapy until PD.

A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Trial site,
- R2-ISS stage at registration (Stage I, Stage II, Stage III, Stage IV, unknown), and
- Response to DRd induction (≥VGPR, <VGPR).

The R2-ISS stage and response to DRd induction will not be entered by research site staff at the point of randomisation. However, the appropriate eCRFs relating to the end of standard of care induction must have been previously completed in order for the participant to proceed to randomisation.

37.4. iFIT2 trial assessments

A tabulated summary of all local and central assessments is provided in Appendix 48.6.

Please refer to the trial eCRFs to ensure you are familiar with all data collection items prior to completing assessments.

37.4.1. Local investigations at the start of each iFIT2 treatment cycle

Within the timeframe of day 1 (or within 5 days prior to day 1) of each treatment cycle, the following local investigations and assessments should be performed (refer to Section 19.7 for criteria for starting each cycle):

- Physical examination (including systolic and diastolic blood pressure, height, weight, vital signs (pulse, O2 saturation, respiratory rate, temperature), and an assessment of visual acuity as indicated, and symptom directed,
- Adverse events assessed by NCI-CTCAE V5 grades (see Section 20 and Appendix 48.5),
- ECOG and Karnofsky performance status (See Appendix 48.4),
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, creatinine, CrCl, and CRP. CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospital is not accurate in older patients,
- Serum paraprotein and immunofixation, SFLC and urinary monoclonal protein detection (quantification where available),
- An assessment of disease response according to the IMWG response criteria (see Appendix 48.2) is required at the end of each cycle of treatment. Samples for this assessment must be taken at, or ≤5 days prior to, cycle 1 day 1 of the next cycle to provide a response. Please note where participant has non-secretory disease adequate imaging and bone marrow sampling to monitor for response and disease progression must be performed,
- Pregnancy test. WCBP (see Appendix 48.10) must have a negative pregnancy test performed by a healthcare professional on day 1 (or ≤3 days prior) of each cycle of treatment (as per the pregnancy prevention plan for lenalidomide),
- Pregnancy prevention counselling, and
- If at any point a first occurrence of CR or sCR is suspected, then it is recommended that a bone marrow aspirate and trephine is sent for local review as well as to HMDS (see Appendix 48.7). CR and sCR cannot be confirmed without bone marrow.

The following assessments are to be carried out for all participants <u>if clinically indicated (standard of care)</u>:

- Cross-sectional imaging according to local practice in accordance with IMWG recommendations for response assessment and NICE guidance and if clinically indicated (standard of care). For monitoring accepted methods include whole body low dose CT, MRI, or PET-CT. MRI spine/pelvis alone is insufficient and should be supplemented by a whole body technique, e.g., whole body low dose CT. Additional imaging is not required by the trial protocol,
- Assessment of cardiac risk, only if clinically indicated as part of standard care, and
- Thyroid function monitoring, only if clinically indicated as part of standard care.

37.4.2. Frailty assessments

Frailty assessments will be carried out for all participants until progression or withdrawal from trial treatment at the following timepoints post-randomisation:

- After 6 cycles of **iFIT2** treatment,
- After 12 cycles of **iFIT2** treatment,
- After 18 cycles of **iFIT2** treatment,
- After 24 cycles of **iFIT2** treatment,
- After 30 cycles of **iFIT2** treatment, and
- After 36 cycles of **iFIT2** treatment.

The frailty assessments to be carried out post-randomisation are as follows:

- IMWG frailty index (Charlson Comorbidity Score, ADL and IADL – Appendix 48.3), and
- ECOG and Karnofsky performance status (Appendix 48.4)

See Section 22.1 regarding source data for these assessments.

37.4.3. Quality of life (QoL) and healthcare resource use questionnaires

Participants will be asked to complete questionnaires at 3, 6, 12, 18, 24, and 30 months post-randomisation. See Section 18.11 for further information.

37.4.4. Central investigations

The following samples should be taken and sent to the following organisations at the specified timepoints.

- RMH/ICR:
  - Bone marrow aspirate (5mL) in EDTA for translational work:
    - At progression,
  - Peripheral blood sample (20mL) in EDTA for translational work **and** clotted blood sample (10mL) in EDTA for translational work:
    - After 6 cycles of **iFIT2** treatment, and
    - At progression.

37.5. Treatment discontinuation after randomisation

Participants are only considered to be off-trial if they have stopped receiving all trial IMPs. If they are still receiving at least one trial IMP, they are considered on-trial.

Participants that discontinue trial treatment following randomisation and before the end of active follow-up will still attend/complete the following assessments until disease progression:

- 2 monthly follow-up to include the local investigations listed in Section 37.4.1,
- Central investigations (see Section 37.4.4), and
- QoL/healthcare resource use questionnaires (see Section 37.4.3).

See Section 18.19 if the treatment discontinuation is due to participant withdrawal. The participant may withdraw from the assessments listed above in addition to the trial treatment.

See Section 18.15 if the treatment discontinuation is due to disease progression.

37.6. Collection and use of email address and/or telephone number

Should participants choose to complete questionnaires online post-randomisation, their email address and/or telephone number will be collected dependent on the method by which they choose to receive

the questionnaires (email and/or text). This information will be stored securely at the CTRU separate to all other iFIT trial data.

38. iFIT2 TRIAL TREATMENTS

See Section 19 for daratumumab, lenalidomide and dexamethasone IMPs.

Participants are randomised to one of the following arms within **iFIT2**:

- Continue DRd until PD, or
- DR (no dexamethasone) until PD.

Where participants are randomised to DR, dexamethasone should be stopped. The only exception will be in the event of an ongoing need for IRR prophylaxis, in which case the minimum necessary dose should be continued once monthly prior to daratumumab. Daratumumab should be reduced to once a month in line with standard of care.

39. iFIT2 STATISTICS AND DATA ANALYSIS

39.1. iFIT2 Sample size calculation

Data from MAIA showed that the median treatment duration for frail patients was 31.1 months [9]. Assuming that treatment duration follows an exponential distribution, this suggests 87% of frail patients were on treatment at 6 months, and 51% were on treatment at 30 months. Therefore, approximately 60% of patients who were on treatment at 6 months remained on treatment at 30 months.

The removal of regular steroid therapy following induction treatment has been shown to improve patient outcomes in NDMM TNE intermediate-fit patients. Larocca *et al*. [97] demonstrated that R compared to Rd after Rd induction increased median EFS by approximately three months, with a hazard ratio of 0.70 (95% CI, 0.51 to 0.95; p = 0.02).

Using the data from MAIA and duration of treatment as a proxy for EFS it is assumed that approximately 60% of patients will be event-free after two-years of maintenance therapy. The minimal clinically important difference for removing regular steroid therapy in this setting is an increase to 75% of patients event-free after 24 months of continuous therapy. This equates to a hazard ratio of 0.54.

Assuming 4 years of recruitment, 2 years of follow-up, 80% power and a two-sided significance level of 5%, 162 patients (81:81) are required with 88 events.

39.2. iFIT2 Statistical analysis

39.2.1. General considerations

A full SAP will be written for **iFIT2** before any analyses are undertaken. Refer to Section 21.3.1 for further details of the general considerations regarding the **iFIT2** statistical analysis.

All analyses will be conducted using the ITT population for **iFIT2**. This population will include participants according to their randomised treatment allocation, regardless of eligibility, whether they prematurely discontinued treatment, or did not comply with the treatment regimen.

If there are a considerable number of protocol violators in **iFIT2**, a per-protocol (PP) analysis will be considered for the primary endpoint. The PP population will exclude participants who do not receive their randomly allocated treatment or who are found to be ineligible following randomisation.

The safety population for **iFIT2** will consist of all participants who received at least one dose of study treatment, according to the treatment received rather than randomised treatment allocation.

39.2.2. Frequency of analysis

Interim statistical summaries will be presented to the DMEC in strict confidence at approximately yearly intervals as described in the DMEC charter.

No formal interim analyses are planned in **iFIT2** before the participants have attained the primary endpoint, which will be triggered by the required number of events (88 events). It is assumed that this will be 2 years following the end of recruitment. Analysis of other endpoints and secondary comparisons will be undertaken alongside this analysis, as appropriate.

39.2.3. Summary of baseline data and flow of patients

The CONSORT [71] flow diagram will be used to summarise the course of participants through the study. Summary tables will show the number of participants in each analysis population by **iFIT2** randomised treatment allocation. Summaries of protocol violations/deviations, including breaches of eligibility criteria and the reasons for non-registrations, non-randomisations, withdrawals, and permanent discontinuation of treatment will also be presented. Additionally, summaries of follow-up time from registration and randomisation will be presented overall and by arm for **iFIT2**.

The characteristics of those randomised into **iFIT2** will be tabulated and appropriately summarised. Each summary will be presented overall and by randomised treatment allocation and will include the information collected on the baseline eCRFs, including, but not limited to:

- Stratification factors used for **iFIT2** randomisation,
- Age (years) at registration,
- Sex,
- Ethnicity,
- IMD,
- ECOG performance status at registration and **iFIT2** baseline,
- Karnofsky performance status at registration and **iFIT2** baseline,
- Paraprotein type,
- Light chain type,
- Immunoglobulin status at registration and **iFIT2** baseline,
- Cytogenetic risk status at registration,
- ISS at registration and **iFIT2** baseline (see Appendix 48.8),
- R-ISS at registration and **iFIT2** baseline (see Appendix 48.8),
- R2-ISS at registration and **iFIT2** baseline (see Appendix 48.8),
- IMWG frailty category at registration (see Appendix 48.3), and
- UK-MRA MRP category at registration and **iFIT2** baseline (see Appendix 48.9).

For **iFIT2**, the post-DRd induction therapy response will also be tabulated. Categorical outcomes will be presented as numbers and percentages, using the total number of forms expected as the denominator; presentation of continuous outcomes will include means, standard deviations, medians, interquartile ranges, and ranges. Missing or unobtainable data will be included as missing in these

summaries unless data are available from the 24-hour randomisation system. No statistical testing will be carried out when summarising these data.

39.2.4. Primary endpoint analysis

Survival curves stratified by randomised treatment allocation, plotting the time since **iFIT2** randomisation against the proportion of participants alive and event-free, and the corresponding 95% confidence intervals will be estimated using the Kaplan-Meier approach. The median PFS times and 95% confidence intervals, overall and by randomised treatment allocation, will be estimated from these plots. The percentages of those alive and progression-free at yearly intervals following **iFIT2** randomisation will also be estimated overall and by randomised treatment allocation along with 95% confidence intervals.

EFS in **iFIT2** will be assessed using Cox proportional hazards regression, adjusting for the stratification factors used in the **iFIT2** randomisation. DRd maintenance to progression will be used as the reference level such that a treatment effect coefficient less than one equates to a reduction in the hazard of an event in the experimental arm. A statistically significant treatment effect will be suggested if the p-value for the corresponding hazard ratio is <0.05. Parameter estimates, hazard ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model.

The proportional hazards assumptions will be assessed by plotting the hazards over time (i.e., the log cumulative hazards plot) for each treatment arm and using appropriate statistical tests. If evidence is found to support the violation of the proportional hazards assumption, then alternative appropriate analysis methods will be investigated.

39.2.5. Secondary endpoint analysis

OS and other time-to-event endpoints will be analysed using methods similar to those described for the primary endpoint.

For both the ORR and maximum response endpoints, the number and proportion of participants in each response category (sCR, CR, VGPR, etc.) will be summarised by randomised treatment allocation and exact 95% confidence intervals will be calculated. The difference in proportions for each response category will be presented with corresponding 95% confidence intervals.

For attainment of ≥VGPR, and other binary endpoints, the number and proportion of participants will be summarised by randomised treatment allocation and exact 95% confidence intervals will be calculated. A logistic regression model will regress the endpoint on randomised treatment allocation, adjusting for the stratification factors used in the **iFIT2** randomisation. Parameter estimates, odds ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model. Residuals and predicted values produced from the models will be examined to assess the assumptions of the statistical models.

Adverse events will be summarised using NCI-CTCAE V5.

Cumulative incidence function curves, plotting time since **iFIT2** randomisation against cumulative incidence of SPMs, overall and stratified by randomised treatment allocation will be estimated along with 95% confidence intervals. Deaths not resulting from SPMs will be considered unrelated for this analysis, and participants affected will be censored at the date of death.

The incidence, type, and grades of infections along with any prophylactic treatment given within **iFIT2** will be summarised descriptively. These will be summarised by randomised treatment allocation where

appropriate. The rate of infections between the experimental and control arms will be analysed using an Anderson-Gill model for recurrent events.

QoL will be summarised using mean scores and 95% CIs for each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role, and functioning domain and for each EORTC QLQ-IL413 item and domain at each assessment timepoint. Similar descriptive summaries will be produced for QALYs, as scored by the EQ-5D-5L questionnaire. Modelling will be conducted to account for the longitudinal nature of the data and the stratification factors, as well as the baseline QoL measurement (end of DRd induction). This, and procedures for missing data, will be detailed in the QoL SAP.

39.2.6. Exploratory endpoint analysis

There are no exploratory objectives currently defined for **iFIT2**, and so no analysis is required.

39.2.7. Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology/serological results, biochemistry results, and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the following endpoints: EFS, PFS, PFS2, OS, attainment of ≥VGPR and attainment of MRD negativity. Note that for the attainment of ≥VGPR and attainment of MRD negativity endpoints, only response subgroups defined before the endpoint timepoint will be analysed. The subgroup analysis of each endpoint will follow the same structure as the main analysis of the respective endpoint where appropriate interaction terms will be added to the regression models to account for the subgroup being investigated.

<u>Patient Characteristics:</u>

- Age (years) at registration (<70, 70 to 80, >80),
- Sex (male, female),
- Ethnicity (White, Mixed, Asian, Black, other, prefer not to say, missing),
- IMD (first, second, third, fourth quartile, missing),
- ECOG performance status at registration (0, 1, ≥2, missing),
- Karnofsky performance status at registration (<80, 80 to 90, >90, missing),
- ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R-ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R2-ISS at registration (Stage I, Stage II, Stage III, Stage IV, missing; see Appendix 48.8), and
- UK-MRA MRP category at registration and **iFIT2** baseline (low, medium, high, missing; see Appendix 48.9).

<u>Haematology/Serological Results:</u>

- Haemoglobin concentration at registration (<100, ≥100g/L),
- White blood cells at registration (<LLN (lower limit of normal), ≥LLN),
- Neutrophil count at registration (<LLN, ≥LLN),
- Lymphocyte count at registration (<LLN, ≥LLN),
- Platelets at registration (<150, ≥150 x 10^9/L), and
- Plasma cells in bone marrow at registration (<60%, ≥60%).

<u>Biochemistry Results:</u>

- β_2M concentration at registration (<3.5, 3.5 to <5.5, ≥5.5mg/L, missing),
- Serum creatinine concentration at registration (<175, ≥175µmol/L, missing),
- Corrected serum calcium concentration at registration (<2.75, ≥2.75mmol/L, missing),
- Serum albumin at registration (<ULN, ≥ULN, missing),
- LDH at registration (<ULN, ≥ULN, missing),

- CRP at registration (<ULN, ≥ULN, missing),
- Total bilirubin* at registration (<ULN, ≥ULN, missing), and
- ALT/AST at registration (<ULN, ≥ULN, missing).

*Except in participants with congenital bilirubinaemia (Gilbert's Syndrome), in which case direct bilirubin will be used.

Cytogenetic/Molecular Results:

- t(4,14) at registration (detected, not detected, not tested),
- t(14,16) at registration (detected, not detected, not tested),
- t(14,20) at registration (detected, not detected, not tested),
- del(17p) at registration (detected, not detected, not tested),
- del(13q) at registration (detected, not detected, not tested),
- del(1p) at registration (detected, not detected, not tested),
- gain(1q) at registration (detected, not detected, not tested),
- Hyperdiploidy at registration (detected, not detected, not tested),
- TP53 mutation status (detected, not detected, not tested),
- IMWG definition risk group at registration (high risk, standard risk), and
- UK definition risk group at registration (ultra-high risk, high risk, standard risk).

Response:

- Response to DRd induction (<VGPR, ≥VGPR),
- Response to **iFIT2** treatment at 6 cycles of treatment (<VGPR, ≥VGPR),
- MRD response to DRd induction (positive, negative, unable to determine), and
- MRD response to **iFIT2** treatment at 6 cycles of treatment (positive, negative, missing).

Further subgroup analyses may be undertaken, as appropriate and all subgroup analysis will be fully documented in the separate **iFIT2** SAP.

Subgroup analyses may, by chance, generate false negative or positive results. Those carried out will be interpreted with caution.

VI. iFIT3 RANDOMISATION PATHWAY

40. iFIT3 BACKGROUND AND RATIONALE

iFIT3 – addressing whether treatment to progression is needed for all patients with an excellent response to induction therapy or whether time limited therapy would be non-inferior

Patients achieving MRD negativity after DRd induction have exceptional longer-term outcomes based on the data from MAIA with the potential for patients to achieve life expectancies approaching that of the general population. Based on these outcomes, all patients entering **iFIT3** will stop dexamethasone for the toxicity reasons outlined above and will be further randomised between continuing DR until disease progression or for a further 18 months (total 2 years) before entering a period of active monitoring off treatment. Time-limited therapy in transplant-eligible myeloma patients with MRD negative response has been reported in the phase II MASTER trial with low rates of disease relapse [99] and is being studied in the current phase III, Cancer Research UK-funded, UK-MRA frontline study for transplant-eligible patients (RADAR (UK-MRA Myeloma XV)) along with others. iFIT will be the first UK trial to address this question in the TNE population. This pathway also addresses the James Lind Alliance priority "How can we safely reduce, cycle, or stop the use of medications to reduce the side effects of treatment and maintain control over myeloma".

41. iFIT3 OBJECTIVES AND ENDPOINTS

41.1. iFIT3 Primary objectives

iFIT3 has co-primary objectives. These are to determine the impact on:

1. PFS (clinical effectiveness), and
2. participant-reported overall health and QoL.

when switching from DR maintenance therapy to progression to DR maintenance therapy for 18 cycles only, in patients who are MRD negative after six cycles of DRd induction therapy.

The clinical effectiveness alternative hypothesis is that DR maintenance therapy for 18 cycles only will result in a reduction in PFS of no more than 10% at 30 months post-randomisation, compared to DR maintenance therapy to progression. The null hypothesis is that the reduction in PFS is more than 10% at 30 months post-randomisation.

The participant-reported overall health and QoL alternative hypothesis is that DR maintenance therapy for 18 cycles only will result in a reduction in the GHS/QoL scale of the EORTC QLQ-C30 questionnaire [1] of no more than 10 points at 30 months post-randomisation, compared to DR maintenance therapy to progression. The null hypothesis is that the reduction in GHS/QoL score is more than 10 points at 30 months post-randomisation.

41.2. iFIT3 Secondary objectives

The secondary objectives are to assess the impact of switching from DR maintenance therapy to progression to DR maintenance therapy for 18 cycles only, in patients who are MRD negative after six cycles of DRd induction therapy, on the following endpoints:

1. Time to progression (TTP),
2. Time to second PFS event (PFS2),
3. Overall survival (OS),
4. Overall response rate (ORR),
5. Attainment of ≥VGPR,
6. Attainment of MRD negativity,
7. Maximum response,
8. Time to improved response,
9. Treatment compliance,
10. Toxicity and safety,
11. Incidence of secondary primary malignancies (SPMs),
12. Incidence, type and rate of infections,
13. Quality of life (QoL), and
14. Cost-utility.

41.3. iFIT3 Exploratory objectives

There are no exploratory objectives currently defined for **iFIT3**.

41.4. iFIT3 Endpoints

Response to treatment, including progression, will be defined using the IMWG response criteria [91] (see Appendix 48.2) for all relevant endpoints.

41.4.1. iFIT3 Primary endpoints

Note that **iFIT3** has co-primary endpoints.

Progression-free survival (PFS)
The time from **iFIT3** randomisation to progression or death from any cause. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Participant-reported overall health and QoL
The QoL score at 30 months after **iFIT3** randomisation. The GHS/QoL scale of the EORTC QLQ-C30 questionnaire [1] will be used to measure QoL.

41.4.2. iFIT3 Secondary endpoints

Time to progression (TTP)
The time from **iFIT3** randomisation to first documented evidence of disease progression. Participants who die without disease progression will be censored at their date of death. Participants alive and progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Time to second PFS event (PFS2)
The time from **iFIT3** randomisation to the second documented evidence of disease progression or death from any cause. Participants alive and for whom a second progression has not been observed at the time of analysis will be censored at their last known date to be alive and second progression-free.

Overall survival (OS)
The time from **iFIT3** randomisation to death from any cause. Participants alive at the time of analysis will be censored at their last known date to be alive.

Overall response rate (ORR)
The categorical response to treatment at key timepoints: sCR, CR, VGPR, PR, MR, SD, or PD. This will be determined at the end of cycle 18 of **iFIT3** treatment, and cycle 30 of **iFIT3** treatment or cycle 12 of **iFIT3** active monitoring, as applicable.

Attainment of ≥VGPR
The binary response to treatment when ORR is dichotomised as ≥VGPR (sCR, CR, VGPR) versus <VGPR (PR, MR, SD, PD). This will be determined at the same key timepoints as ORR.

Attainment of MRD negativity
The binary MRD status, negative versus positive, as assessed by flow cytometry; MRD negativity is defined as at least a serological VGPR and MRD negative bone marrow aspirate at the 10^{-5} threshold. This will be determined at the same key timepoints as ORR.

Maximum response
The maximum response attained at any point after **iFIT3** randomisation.

Time to improved response
The time from **iFIT3** randomisation to first recorded improved response, where the baseline response is that recorded at the start of randomised treatment (**iFIT3** cycle 1, day 1). Participants whose disease progresses or who die before an improved response is recorded will be censored at the time of progression or death, respectively. Participants alive with no improved response recorded at the time of analysis will be censored at their last known date to be alive.

Treatment compliance
Compliance with **iFIT3** treatment will be assessed in multiple ways: a binary variable indicating whether all cycles of treatment were completed, the number of cycles completed, and the total dose of each trial medication received. The number and causes of dose omissions, dose delays, and dose reductions will also be reported, by trial medicinal product.

Toxicity and safety
All AEs, ARs, SAEs, SARs, and SUSARs reported following **iFIT3** randomisation, as graded by NCI-CTCAE V5. Also included are the numbers of pregnancies in both trial participants and their partners where appropriate.

Incidence of secondary primary malignancies (SPMs)
The number of all other cancers, defined as SPMs, reported following **iFIT3** randomisation.

Incidence, type, and rate of infections
In the first instance, this is defined as the proportion of participants in the **iFIT3** pathway experiencing an infection of any type or grade, as graded by NCI-CTCAE V5. Rate of infection is the number of infections experienced divided by the total number of participant days in the **iFIT3** pathway. This will then be extended to consider grade 3, 4, and 5 infections only, and then each type of infection (e.g., fungal, viral, bacterial) separately.

Quality of life (QoL)
Health-related QoL, as scored using the following participant reported questionnaires: EQ-5D-5L, EORTC QLQ-C30 and QLQ-MY20. Participant-reported infections will be assessed using the EORTC QLQ-IL413. QoL questionnaires will be completed at 3, 6, 12, 18, 24, and 30 months post-**iFIT3** randomisation. End of DRd induction is defined as the baseline QoL for **iFIT3**.

Cost-utility
ICERs indicating cost per QALY will be the primary economic evaluation endpoint. Costs will include therapy and healthcare resource use costs. QALYs will be estimated using survival, adjusted for quality

according to the EQ-5D-5L. Probability of cost-effectiveness and net health benefit estimates will also be presented. Willingness to pay for QALY gained will assumed to be in the range £20,000-£30,000 as per NICE guidance.

41.4.3. iFIT3 Exploratory endpoints

There are no exploratory endpoints currently defined for **iFIT3**.

42. iFIT3 TRIAL DESIGN

iFIT3 will assess whether stopping DR therapy after 18 cycles is not detrimental to either PFS or participant-reported overall health and QoL compared to continuing DR to progression in patients who are MRD negative. Eligible participants will be randomly allocated, using a minimisation algorithm with a random element, in a 1:1 ratio to receive DR to progression (standard care), or 18 cycles of DR then stopping. A total of 233 participants are required to be randomised in order to reach the sample size for the powered comparison. Note that **iFIT3** is a non-inferiority comparison with co-primary endpoints.

43. iFIT3 PARTICIPANT ELIGIBILITY

Eligibility waivers to inclusion/exclusion criteria are not permitted.

Confirmation of eligibility for the **iFIT3** pathway must be recorded in the patient's notes. If a participant is not eligible for their assigned **iFIT3** pathway, they cannot continue in the trial at all, i.e., not under any pathway.

43.1. Trial randomisation – iFIT3 pathway

Participants must meet all of the following inclusion criteria and none of the exclusion criteria.

Each participant must only be randomised once.

43.1.1. Inclusion criteria for iFIT3

1. Completed 6 cycles of DRd induction therapy after registering within the iFIT study. Dexamethasone may have been stopped due to toxicity and the participant will remain eligible,
2. Planned to continue on at least daratumumab (monthly) and lenalidomide (at any dose level),
3. Achieved a ≥VGPR and are MRD negative, as confirmed by HMDS,
4. Able to provide full informed consent, and
5. Prepared to comply with pregnancy prevention plan.

43.1.2. Exclusion criteria for iFIT3

1. Received systemic anti-myeloma therapy other than DRd prior to randomisation. Steroids given (by any route) for reasons other than myeloma disease control are allowed,
2. Received a stem cell transplant,
3. Partial response (PR), stable disease (SD) or progressive disease (PD) as per IMWG response criteria (see Appendix 48.2),
4. Pregnant, breast feeding, plans to become pregnant, or plans to father a child whilst enrolled in the study or within 3 months after the last dose, or

5. Participation in any other interventional study for myeloma that involves an IMP during treatment and active monitoring.

44. iFIT3 TRIAL PROCEDURES

The following section should be consulted in line with Section 18.

44.1. Non-randomisation

For participants who do not undergo **iFIT3** randomisation, the reason should be recorded on the applicable eCRF.

Reasons for non-randomisation will be monitored by the CTRU alongside recruitment progress.

44.2. iFIT3 trial randomisation system

iFIT3 randomisation will be performed using the CTRU automated 24-hour web-based system. An authorised PIN will be required for first time users to access the system. They will be provided by the CTRU to staff approved to use the system by the PI on the trial APL, after the research site has received formal approval to open to recruitment. Existing users will access the system using their email and personal password. All registrations and randomisations can be accessed using the following link: https://lictr.leeds.ac.uk/webrand/.

Care must be taken to ensure the correct "randomisation pathway" (**iFIT3**), site code and trial ID are selected/entered to ensure correct randomisation into **iFIT3**.

44.3. iFIT3 randomisation

44.3.1. Consent for iFIT3 randomisation

Once it is known that the participant will be assigned to the **iFIT3** randomisation pathway (expected to be *around* standard of care induction cycle 6 day 28), the potential participant will be provided with a full verbal explanation of the **iFIT3** treatment pathway and be given the **iFIT3** PISICD to consider. It is the responsibility of the research site to ensure that the participant still has a copy of the Study Registration PIS and Additional Information PIS to refer to. Following information provision, participants will be given the opportunity to further discuss the trial with their family and other healthcare professionals before they are asked whether they would be willing to continue their participation in the trial. The right of a participant to refuse to continue their participation in the trial without giving reasons must be respected.

Participants wishing to continue their participation in their assigned **iFIT3** pathway will be required to provide full informed consent using the **iFIT3** ICD.

44.3.2. Eligibility and assessments prior to iFIT3 randomisation

Upon completion of 6 cycles of standard of care induction, after confirmation from CTRU re randomisation pathway assignment, and within 14 days prior to **iFIT3** randomisation, the following local investigations and assessments must be performed to confirm eligibility for randomisation. Note that if randomisation does not occur within 14 days of the assessments following the end of standard

of care induction, then repeat assessments will be required to confirm eligibility (except central bone marrow samples and translational blood sample).

There must be no break in treatment of more than 6 weeks from cycle 6 day 28 of standard of care induction. If treatment is delayed after cycle 6 day 28 for 6 weeks or more, the participant will be considered as off-trial unless discussed and agreed with the CIs, after which point further treatment will be at the discretion of the treating clinician.

Local investigations prior to randomisation

- Review of medical history in line with eligibility criteria for **iFIT3**,
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine, and
- Calculated CrCl (CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospital is not accurate is older patients).

44.3.3. iFIT3 randomisation

Full informed consent for continuation in the trial in the **iFIT3** pathway must be obtained prior to randomisation.

Once participants have given full informed consent and are confirmed eligible, they can be randomised. The participant will continue to use the same trial number as allocated to them at registration.

The following information will be required at randomisation:

- Name of person performing the randomisation,
- Research site name and site code,
- Trial ID number (as allocated at registration),
- Participant details, including initials, date of birth and NHS/CHI number,
- Confirmation of eligibility,
- Confirmation of full informed consent, and
- Email address and/or phone number of participants who choose to complete questionnaires online.

Care must be taken to ensure the correct "randomisation pathway" (iFIT3) , site code and trial ID are selected/entered to ensure correct randomisation into iFIT3.

24-hour iFIT3 randomisation:

https://lictr.leeds.ac.uk/webrand/

Following randomisation, completed **iFIT3** consent forms must be sent via the CTRU Secure File Transfer Service or other CTRU-approved method (never standard e-mail).

Automated confirmation of **iFIT3** randomisation will be emailed to the research site team. The local hospital will provide each participant with a trial ID card, which they should carry with them at all times and present to medical staff should they be admitted to hospital during their time on the trial. Eligibility for **iFIT3** treatment must be confirmed on the relevant eCRF before **iFIT3** treatment can start.

The research site team should notify the participant's GP that they are continuing to take part in the trial under the **iFIT3** pathway using the approved template letter provided by the CTRU. A copy of the letter should be filed in the ISF.

Participants will be randomly allocated on a 1:1 basis to receive either:

- DR (no dexamethasone) therapy until PD, or

- DR (no dexamethasone) therapy for 18 cycles and then active monitoring until PD.

A computer-generated minimisation program that incorporates a random element will be used to ensure treatment groups are well-balanced for the following participant characteristics, details of which will be required for randomisation:

- Trial site,
- IMWG frailty group at the end of DRd induction (FIT, UNFIT, FRAIL), and
- R2-ISS stage at registration (Stage I, Stage II, Stage III, Stage IV, unknown).

The IMWG frailty group, R2-ISS stage, and response to DRd induction will not be entered by research site staff at the point of randomisation. However, the appropriate eCRFs relating to the end of standard of care induction must have been previously completed in order for the participant to proceed to randomisation.

44.4. iFIT3 trial assessments

Please note that participants who are randomised to stop DR treatment, should continue to be assessed on a monthly basis after completion of 18 cycles (i.e., at the same timepoints as participants randomised to DR) until disease progression. This is referred to as active monitoring.

A tabulated summary of all local and central assessments is provided in Appendix 48.6.

Please refer to the trial eCRFs to ensure you are familiar with all data collection items prior to completing assessments.

44.4.1. Local investigations at the start of each iFIT3 treatment/active monitoring cycle

Within the timeframe of day 1 (or within 5 days prior to day 1) of each treatment/active monitoring cycle, the following local investigations and assessments should be performed (refer to Section 19.7 for criteria for starting each cycle):

- Physical examination (including systolic and diastolic blood pressure, height, weight, vital signs (pulse, O2 saturation, respiratory rate, temperature), and an assessment of visual acuity as indicated, and symptom directed,
- AEs assessed by NCI-CTCAE V5 grades (see Section 20 and Appendix 48.5),
- ECOG and Karnofsky performance status (see Appendix 48.4),
- Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, creatinine, CrCl, and CRP. CrCl should be calculated using the Cockcroft-Gault formula as the estimated GFR produced in most hospital is not accurate in older patients,
- Serum paraprotein and immunofixation, SFLC and urinary monoclonal protein detection (quantification where available),
- An assessment of disease response according to the IMWG response criteria (see Appendix 48.2) is required at the end of each cycle of treatment. Samples for this assessment must be taken at, or ≤5 days prior to, cycle 1 day 1 of the next cycle to provide a response. Please note where participant has non-secretory disease adequate imaging and bone marrow sampling to monitor for response and disease progression must be performed,
- Pregnancy test. WCBP (see Appendix 48.10) must have a negative pregnancy test performed by a healthcare professional on day 1 (or ≤3 days prior) of each cycle of treatment (as per the pregnancy prevention plan for lenalidomide),
- Pregnancy prevention counselling, and

- If at any point a first occurrence of CR or sCR is suspected, then it is recommended that a bone marrow aspirate and trephine is sent for local review as well as to HMDS (see Appendix 48.7). CR and sCR cannot be confirmed without bone marrow.

The following assessments are to be carried out for all participants <u>if clinically indicated (standard of care)</u>:

- Cross-sectional imaging according to local practice in accordance with IMWG recommendations for response assessment and NICE guidance and if clinically indicated (standard of care). For monitoring accepted methods include whole body low dose CT, MRI, or PET-CT. MRI spine/pelvis alone is insufficient and should be supplemented by a whole body technique, e.g., whole body low dose CT. Additional imaging is not required by the trial protocol,
- Assessment of cardiac risk, only if clinically indicated as part of standard care, and
- Thyroid function monitoring, only if clinically indicated as part of standard care.

44.4.2. Frailty assessments

Frailty assessments will be carried out for all participants until progression or withdrawal from trial treatment/active monitoring at the following timepoints post-randomisation:

- After 6 cycles of **iFIT3** treatment,
- After 12 cycles of **iFIT3** treatment,
- After 18 cycles of **iFIT3** treatment,
- After 24 cycles of **iFIT3** treatment/after 6 cycles of active monitoring,
- After 30 cycles of **iFIT3** treatment/after 12 cycles of active monitoring, and
- After 36 cycles of **iFIT3** treatment/after 18 cycles of active monitoring.

The frailty assessments to be carried out post-randomisation are as follows:

- IMWG frailty index (Charlson Comorbidity Score, ADL and IADL – Appendix 48.3), and
- ECOG and Karnofsky performance status (Appendix 48.4).

See Section 22.1 regarding source data for these assessments.

44.4.3. Quality of life (QoL) and healthcare resource use questionnaires

Participants will be asked to complete questionnaires at 3, 6, 12, 18, 24, and 30 months post-randomisation. See Section 18.11 for further information.

44.4.4. Central investigations

The following samples should be taken and sent to the following organisations at the specified timepoints.

- <u>HMDS:</u> bone marrow aspirate (5mL) in EDTA for MRD:
  - After 18 cycles of **iFIT3** treatment, and
  - After 30 cycles of **iFIT3** treatment/after 12 cycles of active monitoring,
- <u>RMH/ICR:</u>
  - Bone marrow aspirate (5mL) in EDTA for translational work:
    - At progression, and
  - Peripheral blood sample (20mL) in EDTA for translational work **and** clotted blood sample (10mL) in EDTA for translational work:

- After 6 cycles of **iFIT3** treatment,
- After 18 cycles of **iFIT3** treatment,
- After 30 cycles of **iFIT3** treatment/after 12 cycles of active monitoring, and
- At progression.

44.5. Treatment discontinuation after randomisation

Participants are only considered to be off-trial if:

- They have stopped receiving all trial IMPs when they are expected to receive the trial IMPs, or
- They have withdrawn from active monitoring.

If they are still receiving at least one trial IMP, or have not withdrawn from active monitoring, they are considered on-trial.

Participants that discontinue trial treatment following randomisation and before the end of active follow-up will still attend/complete the following assessments until disease progression:

- 2 monthly follow-up to include the local investigations listed in Section 44.4.1,
- Central investigations (see Section 44.4.4), and
- QoL/healthcare resource use questionnaires (see Section 44.4.3).

See Section 18.19 if the treatment discontinuation is due to participant withdrawal. The participant may withdraw from the assessments listed above in addition to the trial treatment.

See Section 18.15 if the treatment discontinuation is due to disease progression.

44.6. Collection and use of email address and/or telephone number

Should participants choose to complete questionnaires online post-randomisation, their email address and/or telephone number will be collected dependent on the method by which they choose to receive the questionnaires (email and/or text). This information will be stored securely at the CTRU separate to all other iFIT trial data.

45. iFIT3 TRIAL TREATMENTS

See Section 19 for daratumumab, lenalidomide and dexamethasone IMPs.

Participants are randomised to one of the following arms within **iFIT3**:

- DR (no dexamethasone) until PD, **OR**
- DR (no dexamethasone) for 18 cycles, then enter a period of active monitoring until PD.

Daratumumab should be reduced to once a month post-randomisation, in line with standard of care.

Participants randomised to the arm stopping treatment should do so after completion of 18 further cycles.

46. iFIT3 STATISTICS AND DATA ANALYSIS

46.1. iFIT3 Sample size calculation

Clinical effectiveness co-primary endpoint

Data from MAIA showed that almost all MRD negative patients are alive and progression-free at 6 months and that 95% are alive and progression-free at 36 months [12].

It is proposed that an acceptable non-inferiority margin for stopping treatment in terms of PFS is 10% at 1 year after treatment cessation (30 months after completing DRd induction). This has been discussed at a SUAG meeting and was deemed likely to be appropriate, considering the likely availability of efficacious subsequent lines of therapy and the potential benefit of stopping treatment on QoL.

The non-inferiority margin chosen equates to a proportion of MRD negative patients alive and progression-free at 30 months after 6 months DRd induction and 18 months DR maintenance of no less than 85%, compared to 95% of patients after 6 months of DRd induction and continuous DR maintenance. This 10% non-inferiority margin at 30 months equates to a hazard ratio of 3.17. With 4 years of recruitment, 2.5 years of follow-up, 90% power and a one-sided significance level of 2.5%, 226 patients and 40 events are required.

Participant-reported overall health and QoL co-primary endpoint

The GHS/QoL scale of the EORTC QLQ-C30 questionnaire has been chosen as the most appropriate measure for the participant-reported overall health and QoL co-primary endpoint. Although there are symptom- and side-effect-specific scales available for this questionnaire, the responses to these may be biased in favour of one of the two treatment arms.

It is proposed that an acceptable non-inferiority margin for stopping treatment in terms of participant-reported overall health and QoL is 10 points at 1 year after treatment cessation (30 months after **iFIT3** randomisation). This is the minimal clinically relevant difference for a medium effect in QoL [100].

Data from the non-intensive pathway of MRC Myeloma IX (unpublished data) were used to estimate the mean and standard deviation of GHS/QoL scale score at 6 months of DRd induction and 30 months of DR maintenance. The non-inferiority margin chosen equates to a mean GHS/QoL scale score at 30 months, after 6 months DRd induction and 18 months DR maintenance, of no less than 48.3, compared to a mean score of 58.3 in patients after 6 months of DRd induction and continuous DR maintenance. The 226 patients recruited for the PFS co-primary endpoint give 89% power to detect this difference, using the standard deviation of 23.40, as well as a one-sided 2.5% significance level.

46.2. iFIT3 Statistical analysis

46.2.1. General considerations

A full SAP will be written for **iFIT3** before any analyses are undertaken. Refer to Section 21.3.1 for further details of the general considerations regarding to the **iFIT3** statistical analysis.

All analyses will be conducted using the ITT population for **iFIT3**. This population will include participants according to their randomised treatment allocation, regardless of eligibility, whether they prematurely discontinued treatment, or did not comply with the treatment regimen.

Analysis of the primary endpoints will also be conducted on the per-protocol (PP) population for **iFIT3**. The PP population will exclude participants who do not receive their randomly allocated treatment or who are found to be ineligible following randomisation. As randomisation occurs at the start of DR maintenance therapy, participants who fail to reach 18 cycles of DR maintenance will still be included in the PP population. Participants who complete 18 cycles of DR maintenance but fail to take up their

randomised treatment allocation will be excluded. This includes: (a) participants randomised to continue trial treatment after 18 cycles, who do not continue when required to do so by the protocol, and (b) participants randomised to stop trial treatment after 18 cycles, who do not stop when required to do so by the protocol.

Non-inferiority must be demonstrated in both the ITT and the PP populations [101] for cessation of treatment to be deemed non-inferior to continuation.

The safety population for **iFIT3** will consist of all participants who received at least one dose of study treatment, according to the treatment received rather than randomised treatment allocation.

46.2.2. Frequency of analysis

Interim statistical summaries will be presented to the DMEC in strict confidence at approximately yearly intervals as described in the DMEC charter.

A formal interim analysis for futility for **iFIT3** will be conducted when half of the required events (20 events) have been observed, estimated to be 9 months following the end of recruitment. This will be conducted at the 0.0110 significance level [102]. As this analysis is for futility, the significance level for the final analysis will not be adjusted.

A formal interim analysis for feasibility for **iFIT3** will also be conducted at this time. This will use event prediction methods similar to those described by Renfro et al. [103] to estimate the size and number of events observed in the per-protocol population. If the size of the per-protocol population becomes such that the power for either of the co-primary endpoints is reduced to below 80%, equivalent to less than 174 participants, this part of the trial may be halted. Continuous monitoring for feasibility of **iFIT3** will also take place during the trial, with results provided to the oversight committees such that appropriate measures, such as protocol amendments, can be made to prevent loss of study power.

The DMEC, in the light of the interim data, and any advice or evidence they wish to request, will advise the TSC if there is proof beyond reasonable doubt that stopping DR after 18 cycles does result in inferior PFS or that the power for either of the co-primary endpoints is insufficient, and recommend appropriate changes to the trial protocol.

No other formal interim analyses are planned in **iFIT3** before the participants have attained the primary endpoint, which will be triggered by the required number of events (40 events). It is assumed that this will be 2.5 years following the end of recruitment. Analysis of other endpoints and secondary comparisons will be undertaken alongside this analysis, as appropriate.

46.2.3. Summary of baseline data and flow of patients

The CONSORT [71] flow diagram will be used to summarise the course of participants through the study. Summary tables will show the number of participants in each analysis population by **iFIT3** randomised treatment allocation. Summaries of protocol violations/deviations, including breaches of eligibility criteria and the reasons for non-registrations, non-randomisations, withdrawals, and permanent discontinuation of treatment will also be presented. Additionally, summaries of follow-up time from registration and randomisation will be presented overall and by arm for **iFIT3**.

The characteristics of those randomised into **iFIT3** will be tabulated and appropriately summarised. Each summary will be presented overall and by randomised treatment allocation and will include the information collected on the baseline eCRFs, including, but not limited to:

- Stratification factors used for **iFIT3** randomisation,
- Age (years) at registration,

- Sex,
- Ethnicity,
- IMD,
- ECOG performance status at registration and **iFIT3** baseline,
- Karnofsky performance status at registration and **iFIT3** baseline,
- Light chain type,
- Paraprotein type,
- Immunoglobulin status at registration and **iFIT3** baseline,
- Cytogenetic risk status at registration,
- ISS at registration and **iFIT3** baseline (see Appendix 48.8),
- R-ISS at registration and **iFIT3** baseline (see Appendix 48.8),
- R2-ISS at registration and **iFIT3** baseline (see Appendix 48.8),
- IMWG frailty category at registration and **iFIT3** baseline (see Appendix 48.3), and
- UK-MRA MRP category at registration and **iFIT3** baseline (see Appendix 48.9).

For **iFIT3**, the post-DRd induction therapy response will also be tabulated. Categorical outcomes will be presented as numbers and percentages, using the total number of forms expected as the denominator; presentation of continuous outcomes will include means, standard deviations, medians, interquartile ranges, and ranges. Missing or unobtainable data will be included as missing in these summaries unless data are available from the 24-hour randomisation system. No statistical testing will be carried out when summarising these data.

46.2.4. Primary endpoint analysis

Progression-free survival (PFS)

Survival curves stratified by randomised treatment allocation, plotting the time since **iFIT3** randomisation against the proportion of participants alive and progression-free, and the corresponding 95% confidence intervals will be estimated using the Kaplan-Meier approach. The median PFS times and 95% confidence intervals, overall and by randomised treatment allocation, will be estimated from these plots. The percentages of those alive and progression-free at yearly intervals following **iFIT3** randomisation will also be estimated overall and by randomised treatment allocation along with 95% confidence intervals.

PFS in **iFIT3** will be assessed using Cox proportional hazards regression, adjusting for the stratification factors used in the **iFIT3** randomisation. Continuing DR maintenance to progression will be used as the reference level, such that a treatment effect coefficient less than one equates to a reduction in the hazard of death or progression in the experimental arm. A statistically significant treatment effect will be suggested if the upper bound of the 95% confidence interval for the corresponding hazard ratio is <3.17. Parameter estimates, hazard ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model.

The proportional hazards assumptions will be assessed by plotting the hazards over time (i.e., the log cumulative hazards plot) for each treatment arm and using appropriate statistical tests. If evidence is found to support the violation of the proportional hazards assumption, then alternative appropriate analysis methods will be investigated.

Participant-reported overall health and QoL

The GHS/QoL score in **iFIT3** will be summarised using mean scores and 95% CIs at each assessment timepoint.

Multilevel modelling will be conducted to account for the longitudinal nature of the data and the stratification factors used in the **iFIT3** randomisation. Continuing DR maintenance to progression will

be used as the reference level, such that a positive treatment effect coefficient equates to an improvement in participant-reported overall health and QoL in the experimental arm. A statistically significant treatment effect will be suggested if the lower bound of the 95% confidence interval for the corresponding parameter estimate is less than -10. Parameter estimates and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model.

The normality assumption for the GHS/QoL score will be assessed using quantile-quantile plots, by plotting the residuals against both response and each variable and using appropriate statistical tests. If evidence is found to support the violation of the normality assumption, then alternative appropriate analysis methods will be investigated.

46.2.5. Secondary endpoint analysis

OS and other time-to-event endpoints will be analysed using methods similar to those described for the primary PFS endpoint.

For both the ORR and maximum response endpoints, the number and proportion of participants in each response category (sCR, CR, VGPR, etc.) will be summarised by allocated treatment and exact 95% confidence intervals will be calculated. The difference in proportions for each response category will be presented with corresponding 95% confidence intervals.

For attainment of ≥VGPR, and other binary endpoints, the number and proportion of participants will be summarised by randomised treatment allocation and exact 95% confidence intervals will be calculated. A logistic regression model will regress the endpoint on randomised treatment allocation, adjusting for the stratification factors used in the **iFIT3** randomisation. Parameter estimates, odds ratios and corresponding 95% confidence intervals, degrees of freedom, test statistics and p-values will be presented for each variable in the model. Residuals and predicted values produced from the models will be examined to assess the assumptions of the statistical models.

AEs will be summarised using NCI-CTCAE V5.

Cumulative incidence function curves, plotting time since **iFIT3** randomisation against cumulative incidence of SPMs, overall and stratified by randomised treatment allocation will be estimated along with 95% confidence intervals. Deaths not resulting from SPMs will be considered unrelated for this analysis, and participants affected will be censored at the date of death.

The incidence, type, and grades of infections along with any prophylactic treatment given within **iFIT3** will be summarised descriptively. These will be summarised by randomised treatment allocation where appropriate. The rate of infections between the experimental and control arms will be analysed using an Anderson-Gill model for recurrent events.

QoL will be summarised using mean scores and 95% CIs for each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role, and functioning domain and for each EORTC QLQ-IL413 item and domain at each assessment timepoint. Similar descriptive summaries will be produced for QALYs, as scored by the EQ-5D-5L questionnaire. Modelling will be conducted to account for the longitudinal nature of the data and the stratification factors, as well as the baseline QoL measurement. This, and procedures for missing data, will be detailed in the QoL SAP.

46.2.6. Exploratory endpoint analysis

There are no exploratory objectives currently defined for **iFIT3**, and so no analysis is required.

46.2.7. Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology/serological results, biochemistry results, and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the following endpoints: PFS, PFS2, OS, attainment of ≥VGPR and attainment of MRD negativity. Note that for the attainment of ≥VGPR and attainment of MRD negativity endpoints, only response subgroups defined before the endpoint timepoint will be analysed. The subgroup analysis of each endpoint will follow the same structure as the main analysis of the respective endpoint where appropriate interaction terms will be added to the regression models to account for the subgroup being investigated.

Patient Characteristics:

- Age (years) at registration (<70, 70 to 80, >80),
- Sex (male, female),
- Ethnicity (White, Mixed, Asian, Black, other, prefer not to say, missing),
- IMD (first, second, third, fourth quartile, missing),
- ECOG performance status at registration (0, 1, ≥2, missing),
- Karnofsky performance status at registration (<80, 80 to 90, >90, missing),
- IMWG frailty category at registration and **iFIT3** baseline (FIT, UNFIT, FRAIL; see Appendix 48.3),
- ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R-ISS at registration (Stage I, Stage II, Stage III, missing; see Appendix 48.8),
- R2-ISS at registration (Stage I, Stage II, Stage III, Stage IV, missing; see Appendix 48.8), and
- UK-MRA MRP category at registration and **iFIT3** baseline (low, medium, high, missing; see Appendix 48.9).

Haematology/Serological Results:

- Haemoglobin concentration at registration (<100, ≥100g/L),
- White blood cells at registration (<LLN (lower limit of normal), ≥LLN),
- Neutrophil count at registration (<LLN, ≥LLN),
- Lymphocyte count at registration (<LLN, ≥LLN),
- Platelets at registration (<150, ≥150 x 10^9/L), and
- Plasma cells in bone marrow at registration (<60%, ≥60%).

Biochemistry Results:

- β_2M concentration at registration (<3.5, 3.5 to <5.5, ≥5.5mg/L, missing),
- Serum creatinine concentration at registration (<175, ≥175µmol/L, missing),
- Corrected serum calcium concentration at registration (<2.75, ≥2.75mmol/L, missing),
- Serum albumin at registration (<ULN , ≥ULN, missing),
- LDH at registration (<ULN, ≥ULN, missing),
- CRP at registration (<ULN, ≥ULN, missing),
- Total bilirubin* at registration (<ULN, ≥ULN, missing), and
- ALT/AST at registration (<ULN, ≥ULN, missing).

*Except in participants with congenital bilirubinaemia (Gilbert's Syndrome), in which case direct bilirubin will be used.

Cytogenetic/Molecular Results:

- t(4,14) at registration (detected, not detected, not tested),
- t(14,16) at registration (detected, not detected, not tested),
- t(14,20) at registration (detected, not detected, not tested),
- del(17p) at registration (detected, not detected, not tested),

- del(13q) at registration (detected, not detected, not tested),
- del(1p) at registration (detected, not detected, not tested),
- gain(1q) at registration (detected, not detected, not tested),
- Hyperdiploidy at registration (detected, not detected, not tested),
- TP53 mutation status (detected, not detected, not tested),
- IMWG definition risk group at registration (high risk, standard risk), and
- UK definition risk group at registration (ultra-high risk, high risk, standard risk).

Response:

- Response to DRd induction (<VGPR, ≥VGPR),
- Response to **iFIT3** treatment at 18 cycles of treatment (<VGPR, ≥VGPR),
- Response to **iFIT3** treatment at either 30 cycles of treatment, or 18 cycles of treatment and 12 cycles of active monitoring, as appropriate (<VGPR, ≥VGPR),
- MRD response to DRd induction (positive, negative, unable to determine),
- MRD response to **iFIT3** treatment at 18 cycles of treatment (positive, negative, missing), and
- MRD response to **iFIT3** treatment at either 30 cycles of treatment, or 18 cycles of treatment and 12 cycles of active monitoring, as appropriate (positive, negative, missing).

Further subgroup analyses may be undertaken, as appropriate and all subgroup analysis will be fully documented in the separate **iFIT3** SAP.

Subgroup analyses may, by chance, generate false negative or positive results. Those carried out will be interpreted with caution.

VII. REFERENCES AND APPENDICES

47. REFERENCES

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48. APPENDICES

48.1. Definition of myeloma and related disease

The International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma, The Lancet 2014; 15 (12): 538-548 [104]

Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10%, or biopsy-proven bony or extramedullary plasmacytoma*, AND any one or more of the following myeloma defining events:

Myeloma defining events:

- Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcaemia: serum calcium > 0.25mmol/L (>1mg/dL) higher than the upper limit of normal or > 2.75mmol/L (>11mg/dL),
  - Renal insufficiency: creatinine clearance < 40mL per min† or serum creatinine > 177µmol/L (>2mg/dL),
  - Anaemia: haemoglobin value > 20g/L below the lower limit of normal, or a haemoglobin value < 100g/L, or
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡, or
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥ 60%,
  - Involved:uninvolved serum free light chain ratio§ ≥ 100, or
  - > 1 focal lesions on MRI studies¶.

* *Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.*

† *Measured or estimated by validated equations.*

‡ *PET-CT=18F-fluorodeoxyglucose PET with CT. If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement.*

§ *These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100mg/L.*

¶ *Each focal lesion must be 5mm or more in size.*

Definition of plasma cell leukaemia (PCL)

Primary plasma cell leukaemia: consensus definition by the International Myeloma Working Group according to peripheral blood plasma cell percentage, Blood Cancer Journal 2021; 11 (12): 192 [105]

Primary PCL is defined by the presence of 5% or more circulating plasma cells in peripheral blood smears in patients otherwise diagnosed with symptomatic MM. Careful examination of peripheral blood by conventional microscopy should be done in all patients with MM. A minimum of 100–200 nucleated cells per smear should be systematically analysed by an experienced pathologist/haematologist.

Patients with smouldering multiple myeloma, MGUS, solitary plasmacytoma of bone, or solitary extramedullary plasmacytoma are **excluded** from this trial:

Definition of asymptomatic (smouldering) multiple myeloma (Patients with asymptomatic (smouldering) multiple myeloma, MGUS, solitary plasmacytoma of bone, or solitary extramedullary plasmacytoma are excluded from this trial):

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥ 30g/L or urinary monoclonal protein ≥ 500mg per 24h and/or clonal bone marrow plasma cells 10% to 60%, and
- Absence of myeloma defining events or amyloidosis.

Table 21: IMWG diagnostic criteria and classification for monoclonal gammopathy of undetermined significance and related plasma-cell disorders

	Definition[††]	**Progression rate**	**Primary progression events**
Non-IgM monoclonal gammopathy of undetermined significance	Serum monoclonal protein (non-IgM type) < 30g/L Clonal bone marrow plasma cells < 10%* Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder	1% per year	Multiple myeloma, solitary plasmacytoma, immunoglobulin-related amyloidosis (AL, AHL, AH)
IgM monoclonal gammopathy of undetermined significance	Serum IgM monoclonal protein < 30g/L Bone marrow lymphoplasmacytic infiltration < 10% No evidence of anaemia, constitutional symptoms, hyperviscosity, lymphadenopathy, hepatosplenomegaly, or other end-organ damage that can be attributed to the underlying lymphoproliferative disorder	1.5% per year	Waldenström macroglobulinaemia, immunoglobulin-related amyloidosis (AL, AHL, AH)
Light-chain monoclonal gammopathy of undetermined significance	Abnormal FLC ratio (<0·26 or >1.65) Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio > 1.65 and increased λ FLC in patients with ratio < 0·26) No immunoglobulin heavy chain expression on immunofixation Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, and bone lesions (CRAB) or amyloidosis that can be attributed to the plasma cell proliferative disorder Clonal bone marrow plasma cells < 10% Urinary monoclonal protein < 500mg/24h	0.3% per year	Light chain multiple myeloma, immunoglobulin light-chain amyloidosis

	Definition[††]	Progression rate	Primary progression events
Solitary plasmacytoma	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Normal bone marrow with no evidence of clonal plasma cells Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder	About 10% within 3 years	Multiple myeloma
Solitary plasmacytoma with minimal marrow involvement[†]	Biopsy-proven solitary lesion of bone or soft tissue with evidence of clonal plasma cells Clonal bone marrow plasma cells <10% Normal skeletal survey and MRI (or CT) of spine and pelvis (except for the primary solitary lesion) Absence of end-organ damage such as hypercalcaemia, renal insufficiency, anaemia, or bone lesions (CRAB) that can be attributed to a lymphoplasma cell proliferative disorder	60% (bone) or 20% (soft tissue) within 3 years	Multiple myeloma
POEMS syndrome[‡]	Polyneuropathy Monoclonal plasma cell proliferative disorder (almost always λ) Any one of the following three other major criteria: Sclerotic bone lesions Castleman's disease Elevated levels of VEGFA[§] Any one of the following six minor criteria: Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) Extravascular volume overload (oedema, pleural effusion, or ascites) Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic)[¶] Skin changes (hyperpigmentation, hypertrichosis, glomeruloid haemangiomata, plethora, acrocyanosis, flushing, white nails) Papilloedema Thrombocytosis/polycythaemia	NA	NA
Systemic AL amyloidosis[‖**]	Presence of an amyloid-related systemic syndrome (e.g., renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement) Positive amyloid staining by Congo red in any tissue (e.g., fat aspirate, bone marrow, or organ biopsy) Evidence that amyloid is light-chain-related	NA	Some patients might develop multiple myeloma

	Definition††	Progression rate	Primary progression events
	established by direct examination of the amyloid using mass spectrometry-based proteomic analysis, or immunoelectronmicroscopy, and Evidence of a monoclonal plasma cell proliferative disorder (serum or urine monoclonal protein, abnormal free light-chain ratio, or clonal plasma cells in the bone marrow)		

IgM=immunoglobulin M. AL=immunoglobulin light-chain amyloidosis. AHL=immunoglobulin heavy and light-chain amyloidosis. AH=immunoglobulin heavy chain amyloidosis. FLC=free light chain.

* *Bone marrow can be deferred in patients with low-risk monoclonal gammopathy of undetermined significance (IgG type, monoclonal protein < 15g/L, normal free light-chain ratio) in whom there are no clinical features concerning for myeloma.*

† *Solitary plasmacytoma with 10% or more clonal plasma cells is regarded as multiple myeloma.*

‡ *Not every patient meeting these criteria will have POEMS syndrome; the features should have a temporal association with each other and no other attributable cause. Anaemia or thrombocytopenia are distinctively unusual in this syndrome unless Castleman's disease is present.*

§ *The source data do not define an optimal cut-off value for considering elevated VEGFA level as a major criterion. We suggest that VEGFA measured in the serum or plasma should be at least three to four times higher than the normal reference range for the laboratory that is doing the testing to be regarded as a major criterion.*

¶ *To regard endocrinopathy as a minor criterion, an endocrine disorder other than diabetes or hypothyroidism is required because these two disorders are common in the general population.*

‖ *Patients with AL amyloidosis who also meet criteria for multiple myeloma are considered to have both diseases.*

** *About 2% to 3% of patients with AL amyloidosis will not meet the requirement for evidence of a monoclonal plasma cell disorder listed; the diagnosis of AL amyloidosis must be made with caution in these patients.*

†† *All presented criteria must be met for the disease to be diagnosed.*

48.2. IMWG uniform response criteria for multiple myeloma

Blade et al, 1998 ; Durie et al, 2006 ; Rajkumar et al, 2011 ; Kumar S et al, 2016; [91, 106-108].

Fernández de Larrea et al, 2021 [105]

All response categories require 2 consecutive assessments made at any time before the institution of any new therapy. Paraprotein responses should only be calculated using sequential paraprotein measurements made in the same laboratory using the same method. All categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

Where a patient has measurable paraprotein but their paraprotein value is <10g/L at baseline, response assessments should be based on SFLC results where available[c].

Table 22: Disease response and stable disease categories based on IMWG uniform response criteria for multiple myeloma

Response subcategory	Response criteria
Stringent Complete Response (sCR)	- Negative immunofixation on the serum (and urine if measured) **and** - Disappearance of any soft tissue plasmacytomas **and** - <5% plasma cells in bone marrow aspirates[a] **and** - Normal free light chain (FLC) ratio **and** - Absence of clonal cells in the bone marrow biopsy by immunohistochemistry or immunofluorescence[b]
Complete response (CR)	- Negative immunofixation on the serum (and urine if measured) **and** - Disappearance of any soft tissue plasmacytomas **and** - <5% plasma cells in bone marrow aspirates[a] - *Only* in participants *without measurable serum and urine M-protein levels*: a normal FLC ratio of 0.26 to 1.65 (or laboratory-specific normal FLC ratio reference range).
Very Good Partial Response (VGPR)	- Serum (and urine if measured) M-protein detectable by immunofixation but not on electrophoresis **or** - ≥90% reduction in serum M-protein (and urine M-protein level <100mg per 24 hours if measured). - *Only in participants without measurable serum and urine M-protein levels*: ≥90% decrease in the difference between involved and uninvolved FLC levels.
Partial Response (PR)	- ≥50% reduction in serum M-protein (and reduction in urine M-protein level per 24 hours by ≥90% or to <200mg per 24 hours if measured). - *Only* in *participants without measurable serum and urine M-protein levels*: ≥50% decrease in the difference between involved and uninvolved FLC levels. - *Only in participants without measurable serum and urine M-protein levels and without* measurable *FLC levels*: ≥50% decrease in bone marrow plasma cells, provided baseline bone marrow plasma cells percentage was ≥30%. - **In addition to the above listed criteria**, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	- ≥25% but <50% reduction of serum-M protein (and reduction in urine M-protein level per 24 hours by ≥50% but <90% if measured). - [c] *Only* in *participants without measurable serum and urine M-protein levels*: ≥25% but <50% decrease in the difference between involved and uninvolved FLC levels. - **In addition to the above criteria**, if present at baseline, ≥25% but <50% reduction in the size of soft tissue plasmacytomas is also required. - No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).

Stable disease (SD)	- Not meeting the criteria for (s) CR, VGPR, PR, MR or progressive disease (below).

[a] Confirmation with repeat bone marrow biopsy is not needed

b Presence/absence of clonal cells is based upon the K/λ ratio. An abnormal K/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is K/λ of >4:1 or <1:2

c Additional information differs to the IMWG definition

In addition to assessing the disease against the above criteria, participants with plasma cell leukaemia at diagnosis should be assessed against the response criteria for PCL as per Table 23. In practice, patients should have peripheral blood checked for circulating plasma cells by morphology at each cycle until they are no longer detectable, and then repeated if progression is suspected. If stringent complete response is suspected peripheral blood flow cytometry should be performed.

Table 23: Disease response and stable disease categories for plasma cell leukaemia based on the IMWG consensus definition

Response subcategory	Response criteria
Stringent Complete Response (sCR)	- No plasma cells in peripheral blood by flow cytometry.
Complete response (CR) or Very Good Partial Response (VGPR)	- No plasma cells in peripheral blood by morphology.
Partial Response (PR)	- Plasma cells 1-5% in peripheral blood.
Stable disease (SD)	- Not meeting the criteria for (s)CR, VGPR, PR, or progressive disease (below).

Disease progression and relapse categories

All relapse categories require two consecutive assessments made at any time before classification as relapse and/or the institution of new therapy.

Table 24: IMWG uniform response criteria for multiple myeloma: disease progression and relapse categories

Response subcategory	Response criteria
Progressive disease (PD)	Any **<u>one or more</u>** of the following: Increase of ≥25% from lowest confirmed response value in - Serum M-protein (the absolute increase must be ≥5.0g/L)[a]. - Urine M-protein (the absolute increase must be ≥200mg per 24 hours). - *Only in* participants *without measurable serum and urine M-protein levels*: the difference between involved and uninvolved FLC levels. The absolute increase must be >100mg/L. - *Only in participants without measurable serum and urine M-protein levels and without measurable FLC levels*: Bone marrow plasma cell percentage

	(irrespective of baseline status); the absolute percentage must be ≥10%. Appearance of a new lesion(s), ≥50% increase from nadir in SPD[b] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease. NB: In cases of new onset hypercalcaemia suggesting disease progression, imaging should be performed to confirm disease progression.

[a] For progressive disease, serum M-component increases of ≥10g/L are sufficient to define relapse if starting M-component is ≥50g/L.

[b] Plasmacytoma measurements should be taken from the CT portion of the PET/CT.

Serum Free Light Chain (SFLC) escape: Please note in cases where patients had previously serum measurable paraprotein disease but are relapsing with a rise in the difference between involved and uninvolved light chains of >200mg/L on at least two occasions, this will be considered as indicative of SFLC escape and classified as progressive disease. In such cases, details should be forwarded to CTRU in real time for central review and confirmation prior to stopping treatment, unless clinically urgent.

Plasma cell leukaemia: If a participant was diagnosed with plasma cell leukaemia, progressive disease will be defined as an absolute increase of >5% circulating plasma cells.

Measurable Residual Disease Criteria (requires a complete response, as defined above)

In this study, we will monitor flow MRD-negative only.

Table 25: IMWG MRD response criteria for multiple myeloma

Response subcategory	Response criteria
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD-negative at 5 years)[†]
Flow MRD-negative	**Absence of phenotypically aberrant clonal plasma cells by NGF[‡] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher**
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[§] or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue[¶]

MRD tests should be initiated at the time of suspected complete response and as directed in the protocol.

Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1.2.

Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome.

Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable.

Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

In the case where any laboratory value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value achieved for determining time of progression.

48.3. IMWG frailty index

The IMWG frailty index is comprised of the following components: participant age at the time of assessment, the Charlson comorbidity index score (CCI), the Lawton instrumental activities of daily living (IADL), and the Katz index of independence of activities of daily living (ADL). Each component is assessed separately, and then scored accordingly to dictate the IMWG frailty.

Table 26: IMWG frailty index scoring

Component	Score
Age (years)	
≤75	0
76 to 80	1
>80	2
CCI	
≤1	0
≥2	1
IADL	
>5	0
≤5	1
ADL	
>4	0
≤4	1
IMWG frailty	**Total score**
Fit	0 points
Intermediate fitness	1 point
Frail	≥2 points

Using the CCI, each condition present should be scored, and the total score used in the IWMG frailty index scoring.

Table 27: Charlson comorbidity index scoring system; Charlson et al., 1987

Assigned Weight	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral disease (includes aortic aneurysm ≥ 6cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)

2	Hemiplegia Moderate or severe renal disease Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes Tumor without metastasis (exclude if > 5 years from diagnosis) Leukaemia (acute or chronic) Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor AIDS (not just HIV positive)

Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

Using the IADL, for each activity, the criterion which most closely resembles the participant's highest function should be selected, and the total score used in the IMWG frailty index scoring.

Table 28: Lawton instrumental activities of daily living scale (IADL); Lawton and Brody, 1969

Activity	Criteria	Score
Ability to use telephone	Operates telephone on own initiative; looks up and dials numbers	1
	Dials a few well-known numbers	1
	Answers telephone but does not dial	1
	Does not use telephone at all	0
Shopping	Takes care of all shopping needs independently	1
	Shops independently for small purchases	0
	Needs to be accompanied on any shopping trip	0
	Completely unable to shop	0
Food preparation	Plans, prepares, and serves adequate meals independently	1
	Prepares adequate meals if supplied with ingredients	0
	Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0
	Needs to have meals prepared and served	0
Housekeeping	Maintains house alone with occasional assistance (heavy work)	1
	Performs light daily tasks such as dishwashing, bed making	1
	Performs light daily tasks, but cannot maintain acceptable level of cleanliness	1

	Needs help with all home maintenance tasks	1
	Does not participate in any housekeeping tasks	0
Laundry	Does personal laundry completely	1
	Launders small items, rinses socks, stockings, etc.	1
	All laundry must be done by others	0
Mode of transportation	Travels independently on public transportation or drives own car	1
	Arranges own travel via taxi, but does not otherwise use public transportation	1
	Travels on public transportation when assisted or accompanied by others	1
	Travel limited to taxi or automobile with assistance of another	0
	Does not travel at all	0
Responsibility for own medications	Is responsible for taking medications in correct dosages at correct time	1
	Takes responsibility if medication is prepared in advance in separate containers	0
	Is not capable of dispensing own medication	0
Ability to handle finances	Manages financial matters independently (budgets, writes cheques, pays rent and bills, goes to bank); collects and keeps track of income	1
	Manages day-to-day purchases, but needs help with banking, major purchases	1
	Incapable of handling money	0

Using the ADL, for each activity, the level of independence displayed by the participant should be selected, and the total score used in the IMWG frailty index scoring.

Table 29: Katz index of independence in activities of daily living (ADL); Katz et al., 1963

Activity	**Independence: (1 point)** **NO** supervision, direction, or personal assistance	**Dependence: (0 points)** **WITH** supervision, direction, personal assistance, or total care
Bathing	Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area, or disabled extremity.	Needs help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing.
Dressing	Gets clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.	Needs help with dressing self or needs to be completely dressed.

Toileting	Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.	Needs help transferring to the toilet, cleaning self, or uses bedpan or commode.
Transferring	Moves in and out of bed or chair unassisted. Mechanical transferring aides are acceptable.	Needs help in moving from bed to chair or requires a complete transfer.
Continence	Exercises complete control over urination and defecation.	Is partially or totally incontinent of bowel or bladder.
Feeding	Gets food from plate into mouth without help. Preparation of food may be done by another person.	Needs partial or total help with feeding, or requires parenteral feeding.

48.4. ECOG and Karnofsky performance status

Table 30: ECOG performance status; Oken et al., 1982 [109]

Grade	ECOG performance status
0	Fully active, able to carry on all pre-disease performance without any restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair.
5	Dead.

Table 31: Karnofsky performance status; Karnofsky et al., 1949 [110]

Index	Karnofsky performance status
100	Normal, no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort, some signs or symptoms of disease.
70	Cares for self but unable to carry on normal activity or to do active work.
60	Requires occasional assistance but is able to care for most of personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospitalisation is indicated although death not imminent.
20	Very ill; hospitalisation and active supportive care necessary.
10	Moribund.
0	Dead.

48.5. National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE)

Events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events V5 (NCI-CTCAE). A copy is provided in the Investigator Site File and may be obtained at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Published: November 27, 2017

48.6. Schedule of investigations

48.6.1. Induction – all participants

Table 32: Schedule of investigations – induction (all participants)

	Consent and trial registration	**Baseline assessments for eligibility** (within 28 days prior to registration, unless otherwise stated)	**Pre-commencement of DRd induction treatment assessments** (may be cycle 1 day 1 if before treatment begins)	**Assessments on day 1 (or ≤5 days prior) of each DRd induction treatment cycle** (unless otherwise stated)	**Assessments on cycle 3 day 28 (or ≤5 days prior) of DRd induction treatment**	**Assessments on cycle 6 day 15 - 21 of DRd induction treatment** (unless otherwise stated)	**Disease progression**
Pre-trial consent for bone marrow (at time of diagnostic bone marrow) and bone marrow registration	✓						
Full informed consent and trial registration	✓						
Myeloma diagnosis history		✓					
Physical examination (including height, weight, blood pressure, and vital signs)		✓		✓			✓
Medical history (including comorbidities, concomitant medications, and previous malignancies)		✓					
Assessment of cardiac and thyroid function (as part of standard of care)		✓*		✓*			
Laboratory tests including FBC, LFTs, albumin, LDH, U&Es, calcium, creatinine, and IgG.		✓		✓			✓

	Consent and trial registration	**Baseline assessments for eligibility** (within 28 days prior to registration, unless otherwise stated)	**Pre-commencement of DRd induction treatment assessments** (may be cycle 1 day 1 if before treatment begins)	**Assessments on day 1 (or ≤5 days prior) of each DRd induction treatment cycle** (unless otherwise stated)	**Assessments on cycle 3 day 28 (or ≤5 days prior) of DRd induction treatment**	**Assessments on cycle 6 day 15 - 21 of DRd induction treatment** (unless otherwise stated)	**Disease progression**
Urinary protein:creatinine ratio		✓					
Vitamin D (if collected as part of local practice)		✓					
Serum parathyroid hormone (if collected as part of local practice)		✓					
Beta 2 microglobulin (β_2M)		✓			✓	✓	✓
C-Reactive protein (CRP)		✓		✓			✓
Calculated creatinine clearance (CrCl) (using Cockcroft-Gault formula)		✓		✓			
Serology of hepatitis B and C, and HIV		✓					
Pregnancy prevention counselling		✓	At least every 28 days during treatment.				
Pregnancy test		✓ For women of childbearing potential.		✓† For women of childbearing potential.			
Serum paraprotein and immunofixation, serum free light chains (SFLC), and urinary monoclonal protein detection (quantification where available)		✓		✓		✓	✓
Serum total (class-specific) immunoglobulins		✓				✓	✓
Bone marrow aspirate		✓¥				✓¶	✓
Cross-sectional imaging according		✓§		Imaging of lytic and/or focal bone and extramedullary lesions if clinically indicated (standard of care), in accordance with IMWG recommendations and local practice.			

	Consent and trial registration	**Baseline assessments for eligibility** (within 28 days prior to registration, unless otherwise stated)	**Pre-commencement of DRd induction treatment assessments** (may be cycle 1 day 1 if before treatment begins)	**Assessments on day 1 (or ≤5 days prior) of each DRd induction treatment cycle** (unless otherwise stated)	**Assessments on cycle 3 day 28 (or ≤5 days prior) of DRd induction treatment**	**Assessments on cycle 6 day 15 - 21 of DRd induction treatment** (unless otherwise stated)	**Disease progression**
to local practice (accepted methods: whole body low dose CT, MRI, or PET-CT)				Where a participant has non-secretory disease adequate imaging and bone marrow sampling to monitor for response and disease progression must be performed.			
Local cytogenetics report		✓					
<u>Frailty assessments:</u> IMWG frailty index (Charlson comorbidity index, IADL, ADL). ECOG and Karnofsky performance status. iFIT frailty assessments (4 metre timed walk, clinician-led 3-word recall, and clock drawing). G8. Falls within the last 3 months.			✓		✓	✓	
<u>Quality of life (QoL) and healthcare resource use questionnaires:</u> EORTC QLQ-C30, EORTC QLQ-MY20, EORTC QLQ-IL413, EORTC QLQ-IL414 (after 6 cycles only), EQ-5D-5L, STTA (after 6 cycles only), healthcare resource use questionnaire			✓			✓‡	
Infection prevention assessment, including prophylactic medications						✓	

	Consent and trial registration	**Baseline assessments for eligibility** (within 28 days prior to registration, unless otherwise stated)	**Pre-commencement of DRd induction treatment assessments** (may be cycle 1 day 1 if before treatment begins)	**Assessments on day 1 (or ≤5 days prior) of each DRd induction treatment cycle** (unless otherwise stated)	**Assessments on cycle 3 day 28 (or ≤5 days prior) of DRd induction treatment**	**Assessments on cycle 6 day 15 - 21 of DRd induction treatment** (unless otherwise stated)	**Disease progression**
for infection given							
SAEs, SARs, SUSARs, and SPMs	**Refer to Section 20**. All SUSARs, SARs, and SAEs (including SPMs) must be reported to CTRU **within 24 hours** of the site becoming aware of the event. SAEs must be reported from trial registration, until 60 days after last treatment dose or 60 days after last cycle of active monitoring, as appropriate. SUSARs and SARs must be reported from trial registration, for the duration of the trial.						

* Only if clinically indicated.

† Pregnancy tests must be performed on day 1 (or ≤3 days prior) of each DRd induction treatment cycle.

¥ If the participant did not consent to the pre-trial bone registration part of iFIT, the bone marrow biopsy must be taken after full informed consent. Local bone marrow aspirate confirming myeloma diagnosis must be dated within 12 weeks prior to the date of main trial registration. Central bone marrow samples must be dated within 14 weeks prior to the start of treatment. If the bone marrow aspirate falls out of the specified timeline it will need to be repeated.

§ Imaging within 14 weeks prior to trial registration is mandatory. It is not necessary to repeat imaging if last performed within **14 weeks** of registration, unless clinically indicated.

‡ Quality of life (QoL) and healthcare resource questionnaires at the end of cycle 6 of DRd induction should be given as close to day 28 as possible, but must be done before iFIT pathway randomisation or non-randomisation.

¶If the participant has an unmonitorable phenotype, as confirmed by CTRU, they are not required to have a bone marrow sample taken during cycle 6.

48.6.2. Randomisation iFIT1, iFIT2 or iFIT3 – all participants who are randomised

Table 33: Schedule of investigations – randomisation (all participants randomised)

	Consent and iFIT randomisation	**iFIT baseline assessments for eligibility** (within 14 days prior to registration, unless otherwise stated)	**Day 1 (or ≤5 days prior) to each cycle of randomised treatment or active monitoring**	**Follow-up for participants coming off study prior to disease progression: every 2-months**	**Disease progression**
Full informed consent and iFIT randomisation	✓				
Review of medical history (including other previous malignancies) in line with eligibility criteria		✓			
Serology of hepatitis B and C, and HIV (**iFIT1** only)		✓			
Physical examination (including height/weight, blood pressure, vital signs)			✓		✓
Assessment of cardiac and thyroid function (as part of standard of care)		✓* Cardiac assessment required for **iFIT1** only.	✓*	✓*	
Assessment of CRS and ICANS (including neurological examination and ICE score)			✓^		
Laboratory tests including FBC, U&Es, LDH, albumin, calcium, creatinine, and LFTs		✓	✓§		✓
Calculated creatinine clearance (CrCl) (using Cockcroft-Gault formula)		✓	✓		✓
Beta 2 microglobulin (β_2M)					✓
C-Reactive protein (CRP)		✓	✓		✓
ECOG and Karnofsky performance status			✓		✓
Serum paraprotein and immunofixation, serum free light chains (SFLC), and urinary monoclonal protein detection (quantification where available)		✓	✓	✓δ	✓
Serum total (class-specific) immunoglobulins			✓ **iFIT1** only.	✓ **iFIT1** only.	✓

	Consent and iFIT randomisation	**iFIT baseline assessments for eligibility** (within 14 days prior to registration, unless otherwise stated)	**Day 1 (or ≤5 days prior) to each cycle of randomised treatment or active monitoring**	**Follow-up for participants coming off study prior to disease progression: every 2-months**	**Disease progression**
Pregnancy prevention counselling			✓ At least every 28 days during lenalidomide treatment		
Pregnancy test		✓ For women of childbearing potential on lenalidomide	✓† For women of childbearing potential on lenalidomide		
Bone marrow aspirate and (if available) trephine‖			✓	✓δ	✓
Cross-sectional imaging according to local practice (accepted methods: whole body low dose CT, MRI, or PET-CT)			Imaging of lytic and/or focal bone and extramedullary lesions if clinically indicated (standard of care), in accordance with IMWG recommendations and local practice. Where a participant has non-secretory disease adequate imaging and bone marrow sampling to monitor for response and disease progression must be performed.		
<u>Frailty assessments:</u> IMWG frailty index (Charlson comorbidity index, IADL, ADL). ECOG and Karnofsky performance status.			✓ Every 6 cycles up to 36 cycles (treatment/active monitoring)		
<u>Quality of life (QoL) and healthcare resource use questionnaires:</u> EORTC QLQ-C30, QLQ-MY20, EORTC QLQ-IL413, EQ-5D-5L, EORTC QLQ-IL414 (**iFIT1** only), STTA (**iFIT1** only), healthcare resource use questionnaire			✓‖	✓‖	
Infection prevention assessment, including vaccination history and prophylactic medications for infection given (**iFIT1** only)			✓		
AEs, ARs, AESIs and Special Situations, SAEs, SARs, SUSARs, and SPMs	**Refer to Section 20**. All SUSARs, SARs, and SAEs (including SPMs) must be reported to CTRU **within 24 hours** of the site becoming aware of the event. SAEs must be reported from trial registration, until 60 days after last treatment dose or 60 days				

	Consent and iFIT randomisation	**iFIT baseline assessments for eligibility** (within 14 days prior to registration, unless otherwise stated)	**Day 1 (or ≤5 days prior) to each cycle of randomised treatment or active monitoring**	**Follow-up for participants coming off study prior to disease progression: every 2-months**	**Disease progression**
	after last cycle of active monitoring, as appropriate. SUSARs and SARs must be reported from trial registration, for the duration of the trial. All AESIs and Special Situations must be reported to CTRU **within one working day**. AESIs and Special Situations must be reported from the first dose until 60 days after the last dose of teclistamab/talquetamab or 60 days after the last cycle of active monitoring, as appropriate.				

* Only if clinically indicated.

^ CRS and ICANS must be assessed, including reporting neurological examination and ICE score, before each step-up dose, each first maintenance dose, and on cycle 2 day 1, for participants in **iFIT1** receiving teclistamab and talquetamab.

§ For participants in **iFIT1** receiving teclistamab and talquetamab, safety bloods (including FBC, coagulation, U&Es, and LFTs) should be repeated before each dose in the step-up phase and doses delayed in the event of toxicity (see Table 15 and Table 17).

δ If performed as standard of care.

† Pregnancy tests must be performed on day 1 (or ≤3 days prior) of each treatment cycle which includes lenalidomide.

⁋ If at any point a first occurrence of CR or sCR is suspected, then bone marrow aspirate and trephine should be sent for local review as well as to HMDS, as detailed below. CR and sCR cannot be confirmed without bone marrow.

¥ If the participant did not consent to the pre-trial bone registration part of iFIT, the bone marrow biopsy must be taken after full informed consent. Local bone marrow aspirate confirming myeloma diagnosis must be dated within 12 weeks prior to the date of main trial registration. Central bone marrow samples must be dated within 14 weeks prior to the start of treatment. If the bone marrow aspirate falls out of the specified timeline it will need to be repeated.

‖ Quality of life (QoL) and healthcare resource questionnaires should be given at 3, 6, 12, 18, 24, and 30 months post-randomisation.

48.6.3. Sample collection for central investigations

Table 34: Sample collection for central investigations (all participants via core consent)

Sample	Send to	Investigation	Registration	Standard of care induction DRd cycle 6	After cycle 6 of iFIT1 / iFIT2 / iFIT3 treatment	After cycle 18 of iFIT1 / iFIT3 treatment	After cycle 30 of iFIT1 / iFIT3 treatment **OR** after cycle 12 of iFIT1 / iFIT3 active monitoring	Disease Progression
5mL bone marrow aspirate in EDTA	HMDS, Leeds	To determine MRD	✓ (after bone marrow registration **or** trial registration)	✓		✓	✓	
5mL bone marrow aspirate in EDTA	RMH/ICR, London*	Tumour and tumour / microenvironment therapy resistance biology	✓ (after bone marrow registration **or** trial registration)	✓ first 400 participants only		✓ first 300 participants in **iFIT1** only		✓
20mL peripheral blood in EDTA		Host biology and depth of response studies	✓ (trial registration)	✓	✓	✓	✓	✓
10mL clotted blood			✓ (trial registration)	✓	✓	✓	✓	✓

*Samples sent to RMH/ICR by sites will be shared with LIMR via RMH/ICR.

48.7. Central laboratory addresses for sending samples

Table 35: Central laboratory addresses for sending samples

Haematology Malignancy Diagnostic Service (HMDS), Leeds	Haematology Malignancy Diagnostic Service (HMDS) Level 03, Bexley Wing St James's University Hospital Leeds LS9 7TF **Tel:** 0113 206 7851 **Email:** leedsth-tr.hmdsclinicaltrials@nhs.net *Email address for ordering safeboxes from HMDS (with pre-paid postage): CTRU-iFIT@leeds.ac.uk*
The Royal Marsden NHS Foundation Trust/Institute of Cancer Research (RMH/ICR)	Centre for Myeloma Research Division of Molecular Pathology Institute of Cancer Research Brookes Lawley Building 15 Cotswold Road London, Surrey SM2 5NG **Email:** myeloma.lab@icr.ac.uk *Email address for ordering safeboxes from RMH/ICR (with pre-paid postage): CTRU-iFIT@leeds.ac.uk*

48.8. International staging system for multiple myeloma and its revisions (ISS, R-ISS, R2-ISS)

Table 36: International staging system (ISS) for multiple myeloma; Greipp et al., 2005 [45]

ISS stage	Criteria
I	Serum β_2 microglobulin <3.5mg/L; serum albumin ≥3.5g/dL
II	Not ISS stage I or III
III	Serum $ß_2$ microglobulin ≥5.5mg/L

Table 37: Revised international staging system (R-ISS) for multiple myeloma; Palumbo et al., 2015 [46]

Prognostic factor	Criteria
ISS stage	As in Table 36.
CA by iFISH	
High risk	Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16)
Standard risk	Not high-risk
LDH	
Normal	Serum LDH ≤ the upper limit of normal
High	Serum LDH > the upper limit of normal
R-ISS stage	
I	ISS stage I and standard-risk CA by iFISH and normal LDH
II	Not R-ISS stage I or III
III	ISS stage III and either high-risk CA by iFISH or high LDH

Table 38: Second revision of the international staging system (R2-ISS) for multiple myeloma; D'Agostino et al., 2022 [47]

Prognostic factor	Criteria	Risk score
ISS stage		
I	As in Table 36.	0
II		1
III		1.5
CA by iFISH		
del(17p)		1
translocation t(4;14)		1
1q+		0.5
LDH		
Normal	Serum LDH ≤ the upper limit of normal	0
High	Serum LDH > the upper limit of normal	1
R2-ISS stage	**Total score**	
I	0 points	
II	0.5 to 1 points	
III	1.5 to 2.5 points	
IV	3 to 5 points	

Abbreviations:

CA *- chromosomal abnormalities*

iFISH *- interphase fluorescent in situ hybridization*

LDH *- lactate dehydrogenase*

48.9. UK Myeloma Research Alliance Risk Profile

Cook *et al., A clinical prediction model for outcome and therapy delivery in transplant-ineligible patients with myeloma (UK Myeloma Research Alliance Risk Profile): a development and validation study. The Lancet Haematology, 2019, 6 (3), e154-e166. [4]*

Table 39: UK-MRA risk profile scoring

Prognostic factor	Score
WHO performance status	
0	-0.398
1	-0.199
2	0.000
3	0.199
4	0.397
Age (years)	$\frac{\text{Age} - 74.4}{5.40} \times 0.089$
ISS stage	
I	-0.212
II	0.000
III	0.212
CRP	$\frac{\log_e(\text{CRP} + 1) - 2.08}{1.11} \times 0.035$
MRP category	**Total score**
Fit	MRP score < 0.256
Intermediate fitness	-0.256 ≤ MRP score ≤ -0.0283
Frail	-0.0283 < MRP score

Abbreviations:

WHO *– World Health Organization*

ISS *- International Staging System*

CRP *– C-reactive protein (mg/L)*

48.10. Definitions of childbearing and non-childbearing potential and effective methods of contraception

Women not of childbearing potential include women who:

- Are age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year (amenorrhoea following cancer therapy or during breast-feeding does not rule out childbearing potential),
- Or have
    - *Premature ovarian failure confirmed by a specialist gynaecologist,*
    - *Previous bilateral salpingo-oophorectomy, or hysterectomy, or*
    - *XY genotype, Turner syndrome, uterine agenesis.*

Women of childbearing potential (WCBP) are all women who do not meet the above criteria even those who abstain from sexual intercourse.

Effective methods of contraception:

The following can be considered to be examples of suitable methods of contraception:

- Implant,
- Levonorgestrel-releasing intrauterine system,
- Medroxyprogesterone acetate depot,
- Tubal sterilization,
- Sexual intercourse with a vasectomised male partner only; vasectomy must be confirmed by two negative semen analyses, and
- Ovulation inhibitory progesterone-only pills (i.e., desogestrel).

Because of the increased risk of VTE in participants with MM, combined oral contraceptive pills are not recommended. If a participant is currently using combined oral contraception, she should switch to one of the effective methods listed above. The risk of VTE continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Insertion of copper-releasing intrauterine devices are generally not recommended due to the potential risks of infection at the time of insertion and menstrual blood loss which may compromise patients with neutropenia or thrombocytopenia.

48.11. Protocol amendment history

This is v1.0 of the protocol. No prior amendments have been made.

48.12. Safety monitoring plan for daratumumab, lenalidomide and dexamethasone

Risks associated with trial interventions

X A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):*

The combination daratumumab, lenalidomide and dexamethasone (DRd) is the UK standard of care, having been approved by the Scottish Medicine Consortium in September 2023 and NICE in October 2023. The dosing used in iFIT will be in accordance with the standard of care.

The known risks and benefits to participants are well studied and available in the SmPC.

The trial is therefore categorised as **Type A = comparable to the risk of standard medical care**

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		**How will these risks be minimised?**		
IMP/Intervention	**Body System/Hazard**	**Activity**	**Frequency**	**Comments/ Section**
Daratumumab	Injection related reactions	Advice regarding prophylaxis and management included in protocol	Common	19.8 and 19.10.1
Daratumumab	Interference with indirect antiglobulin test	Advice regarding appropriate steps to minimise risk included in protocol	Common	19.10.1
Lenalidomide	Arterial and venous thromboembolic events	Advice regarding prophylaxis included in protocol	Common	19.10.2
Lenalidomide	Teratogenicity	Advice regarding pregnancy prevention included in protocol	Rare	Inclusion/ exclusion criteria and 19.13.1
Lenalidomide	Second primary malignancies	Monitoring and reporting	Common	20.5
Daratumumab and lenalidomide	Infection	Advice regarding prophylaxis included in protocol	Common	19.12
Daratumumab and lenalidomide	Cytopenias	Advice regarding pre-treatment levels prior to commencing	Common	19.7 and 19.9.4

		each cycle and toxicity management included in protocol		

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g., DMEC, independent data review, etc.)

A DMEC will be convened for the trial, who will meet on an annual basis and will review interim unblinded safety information for the trial as agreed by the committee at their initial meeting. Full interim reports will be presented to the DMEC in confidence annually. The DMEC will, in light of these reports, have the authority to recommend trial closure to the TSC should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend appropriate action including amendments to or closure of the trial at any time.

Participant data will be entered on to a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. Validation checks will be incorporated into the trial database to verify the data, and discrepancy reports will be generated for resolution by the research site. Priority validations will be incorporated to ensure that any discrepancies related to participant rights, or the safety of participants, are expedited to research sites for resolution.

48.13. Safety monitoring plan for teclistamab and talquetamab

Risks associated with trial interventions

☐ A ≡ Comparable to the risk of standard medical care

X B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: *Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):*

Some higher risks than standard medical care due to the risk of cytokine release syndrome and ICANS with teclistamab and talquetamab that require close monitoring and management. Higher risk of infection with teclistamab that with standard medical care.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		**How will these risks be minimised?**		
IMP/Intervention	**Body System/Hazard**	**Activity**	**Frequency**	**Comments/ Section**
Teclistamab and talquetamab	Infection	Advice regarding prophylaxis included in protocol	Common	31.10.1
Talquetamab	Oral toxicity, weight loss and skin reactions	Advice regarding management included in protocol	Common	31.10.2
Teclistamab and Talquetamab	CRS and ICANS	Exclusion of patients at highest risk. Advice regarding prophylaxis, monitoring, and management of CRS/ICANS included in protocol	Common	29 and 31
Teclistamab and Talquetamab	Cytopenias	Advice regarding monitoring and management included in protocol	Common	31

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g., DMEC, independent data review, etc.)

A DMEC will be convened for the trial, who will meet on an annual basis and will review interim unblinded safety information for the trial as agreed by the committee at their initial meeting. Safety information will be reviewed at least 6 monthly whilst participants remain on treatment. Full interim reports will be presented to the DMEC in confidence annually. The DMEC will, in light of these reports, have the authority to recommend trial closure to the TSC should they have concerns over the safety or ethics of the trial. The TSC have the authority to recommend appropriate action including amendments to or closure of the trial at any time.

Participant data will be entered on to a validated database and monitored for completeness and quality by the CTRU. Missing data will be chased until it is received, confirmed as not available, or the trial is at analysis. Validation checks will be incorporated into the trial database to verify the data, and discrepancy reports will be generated for resolution by the research site. Priority validations will be incorporated to ensure that any discrepancies related to participant rights, or the safety of participants, are expedited to research sites for resolution.

48.14. Dose banding for teclistamab and talquetamab

48.14.1. Teclistamab dose banding

Table 40: Teclistamab dose banding: injection volumes (10mg/mL) for step-up dose 1 (0.06mg/kg)

Injection volumes of TECVAYLI (10mg/mL) for Step-up dose 1 (0.06mg/kg)				
Step-up dose 1 (0.06mg/kg)	**Body weight (kg)**	**Total dose (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 3mL)**
	35-39.9	2.2	0.22	1
	40-44.9	2.5	0.25	1
	45-49.9	2.8	0.28	1
	50-59.9	3.3	0.33	1
	60-69.9	3.9	0.39	1
	70-79.9	4.5	0.45	1
	80-89.9	5.1	0.51	1
	90-99.9	5.7	0.57	1
	100-109.9	6.3	0.63	1
	110-119.9	6.9	0.69	1
	120-129.9	7.5	0.75	1
	130-139.9	8.1	0.81	1
	140-149.9	8.7	0.87	1
	150-160	9.3	0.93	1
If mandatory per site procedures, calculations can be performed per site practices.				

Table 41: Teclistamab dose banding: injection volumes (10mg/mL) for step-up dose 2 (0.3mg/kg)

Injection volumes of TECVAYLI (10mg/mL) for Step-up dose 2 (0.3mg/kg)				
	Body weight (kg)	**Total dose (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 3mL)**
Step-up dose 2 (0.3mg/kg)	35-39.9	11	1.1	1
	40-44.9	13	1.3	1
	45-49.9	14	1.4	1
	50-59.9	16	1.6	1
	60-69.9	19	1.9	1
	70-79.9	22	2.2	1
	80-89.9	25	2.5	1
	90-99.9	28	2.8	1
	100-109.9	31	3.1	2
	110-119.9	34	3.4	2
	120-129.9	37	3.7	2
	130-139.9	40	4.0	2
	140-149.9	43	4.3	2
	150-160	47	4.7	2
If mandatory per site procedures, calculations can be performed per site practices.				

Table 42: Teclistamab dose banding: injection volumes (90mg/mL) for first maintenance doses (1.5mg/kg)

Injection volumes of TECVAYLI (90mg/mL) for first maintenance doses (1.5mg/kg)				
	Body weight (kg)	**Total dose (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.7mL)**
Maintenance dose (1.5mg/kg)	35-39.9	56	0.62	1
	40-44.9	64	0.71	1
	45-49.9	71	0.79	1
	50-59.9	83	0.92	1
	60-69.9	99	1.1	1
	70-79.9	108	1.2	1
	80-89.9	126	1.4	1
	90-99.9	144	1.6	1
	100-109.9	153	1.7	1*
	110-119.9	171	1.9	2
	120-129.9	189	2.1	2
	130-139.9	198	2.2	2
	140-149.9	216	2.4	2
	150-160	234	2.6	2
*By common practice, each 150mg (90mg/mL) IP vial contains sufficient overfill to deliver the 153mg dose (1.7mL) for the 100-109.9 body weight category, thus necessitating the use of only 1 vial of the 90mg/mL IP. If mandatory per site procedures, calculations can be performed per site practices.				

Table 43: Teclistamab dose banding: injection volumes (90mg/mL) for first maintenance doses (3mg/kg)

Injection volumes of TECVAYLI (90mg/mL) for first maintenance doses (3mg/kg)				
	Body weight (kg)	**Total dose (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.7mL)**
Maintenance dose (3mg/kg)	35-39.9	108	1.2	1
	40-44.9	126	1.4	1
	45-49.9	144	1.6	1
	50-59.9	162	1.8	2
	60-69.9	198	2.2	2
	70-79.9	225	2.5	2
	80-89.9	252	2.8	2
	90-99.9	288	3.2	2
	100-109.9	315	3.5	3
	110-119.9	342	3.8	3
	120-129.9	378	4.2	3
	130-139.9	405	4.5	3
	140-149.9	432	4.8	3
	150-160	468	5.2	4
If mandatory per site procedures, calculations can be performed per site practices.				

48.14.2. Talquetamab dose banding

Table 44: Talquetamab dose banding: injection volumes (2mg/mL) for 0.01mg/kg dose

0.01mg/kg dose: injection volumes using TALVEY 2mg/mL vial				
	Body weight (kg)	**Total dose[a] (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.5mL)**
0.01mg/kg dose	35-39	0.38	0.19	1
	40-45	0.42	0.21	1
	46-55	0.5	0.25	1
	56-65	0.6	0.3	1
	66-75	0.7	0.35	1
	76-85	0.8	0.4	1
	86-95	0.9	0.45	1
	96-105	1.0	0.5	1
	106-115	1.1	0.55	1
	116-125	1.2	0.6	1
	126-135	1.3	0.65	1
	136-145	1.4	0.7	1
	146-155	1.5	0.75	1
	156-160	1.6	0.8	1
[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL). If mandatory per site procedures, calculations can be performed per site practices.				

Table 45: Talquetamab dose banding: injection volumes (2mg/mL) for 0.06mg/kg dose

0.06mg/kg dose: injection volumes using TALVEY 2mg/mL vial				
	Body weight (kg)	**Total dose[a] (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.5mL)**
0.06mg/kg dose	35-39	2.2	1.1	1
	40-45	2.6	1.3	1
	46-55	3	1.5	1
	56-65	3.6	1.8	2
	66-75	4.2	2.1	2
	76-85	4.8	2.4	2
	86-95	5.4	2.7	2
	96-105	6	3	2
	106-115	6.6	3.3	3
	116-125	7.2	3.6	3
	126-135	7.8	3.9	3
	136-145	8.4	4.2	3
	146-155	9	4.5	3
	156-160*	9.6	4.8	4

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL).
*This range includes up to 160.9kg.
If mandatory per site procedures, calculations can be performed per site practices.

Table 46: Talquetamab dose banding: injection volumes (40mg/mL) for 0.4mg/kg dose

0.4mg/kg dose: injection volumes using TALVEY 40mg/mL vial				
	Body weight (kg)	**Total dose[a] (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.0mL)**
0.4mg/kg dose	35-39	14.8	0.37	1
	40-45	16	0.4	1
	46-55	20	0.5	1
	56-65	24	0.6	1
	66-75	28	0.7	1
	76-85	32	0.8	1
	86-95	36	0.9	1
	96-105	40	1	1
	106-115	44	1.1	2
	116-125	48	1.2	2
	126-135	52	1.3	2
	136-145	56	1.4	2
	146-155	60	1.5	2
	156-160	64	1.6	2

[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL).
If mandatory per site procedures, calculations can be performed per site practices.

Table 47: Talquetamab dose banding: injection volumes (40mg/mL) for 0.8mg/kg dose

0.8mg/kg dose: injection volumes using TALVEY 40mg/mL vial				
	Body weight (kg)	**Total dose[a] (mg)**	**Volume of injection (mL)**	**Number of vials (1 vial = 1.0mL)**
0.8mg/kg dose	35-39	29.6	0.74	1
	40-45	34	0.85	1
	46-55	40	1	1
	56-65	48	1.2	2
	66-75	56	1.4	2
	76-85	64	1.6	2
	86-95	72	1.8	2
	96-105	80	2	2
	106-115	88	2.2	3
	116-125	96	2.4	3
	126-135	104	2.6	3
	136-145	112	2.8	3
	146-155	120	3	3
	156-160	128	3.2	4
[a] The Total dose (mg) is calculated based on the rounded Volume of injection (mL). If mandatory per site procedures, calculations can be performed per site practices.				