University Hospitals Coventry and Warwickshire NHS Trust

STATISTICAL ANALYSIS PLAN

UK FixDT: UK **Fix**ation of **D**istal **T**ibia Fractures

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Ethical approval

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Registration

The study is registered with the current controlled trials database under reference number ISRCTN99771224

Dates

Study start date: 01/03/2013

Study end date: 28/02/2017

1. CONTENTS

2. CONTACT DETAILS

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3. BACKGROUND

A comprehensive summary of the background to the trial can be found in the **FixDT protocol**.

The tibia is the most commonly broken major bone in the leg. Injuries usually require hospital admission, frequently require surgery and result in prolonged periods (months) away from work and social activities.

The treatment of displaced, extra-articular fractures of the distal tibia (lower third) remains controversial. These injuries are difficult to manage due to the limited soft tissue cover, poor vascularity of the area and proximity of the fracture to the ankle joint. Infections, non-union and malunion are well-recognised complications.

Surgical treatment options include locked intramedullary nails, plate and screw fixation and external fixator systems including the Ilizarov frame and hybrid fixators. External fixators may be beneficial in selected cases – particularly those with severe soft-tissue injuries - but the **nail and plate options are the most common in the UK**. Mid-shaft fractures of the tibia are generally successfully treated with locked intramedullary nails. However, in the more distal metaphyseal region of the tibia the fixation may be less stable. The nail or screws which are inserted into the nail may break, mal-alignment may occur and there is a risk that the nail will penetrate into the ankle joint.

A recent pilot RCT of locking plate versus medullary nail fixation involving 24 patients with isolated extra-articular fractures of the distal tibia, using the Disability Rating Index (DRI) at 6 months as the primary outcome, found some evidence in favour of the intramedullary nail group. This pilot study provided compelling evidence to support the development of a definitive randomised trial in multiple centres.

4. PROTOCOL SUMMARY

4.1 Trial summary

The project is a **two-phased study. Phase 1 (Feasibility phase)** assessed the feasibility of running a large-scale multi-centre randomised controlled trial in this complicated area of trauma research. **Phase 2 (Main phase)** will undertake the proposed randomised controlled trial in a minimum of 18 trauma centres across the UK.

Feasibility

The pilot will take place in **6 centres over a period of 6 months**. The main aim of this initial phase will be to determine the number of eligible and recruited patients in the trauma centres over the course of 6 months. Screening logs will be kept at each site to determine the number of patients assessed for eligibility and reasons for any exclusion. In addition, the number of eligible and recruited patients, and the number of patients who decline consent/withdraw, will be recorded.

Main RCT

All adult patients presenting at the trial centres with an isolated, acute fracture of the distal tibia are potentially eligible to take part in the trial. The broad eligibility criteria will ensure that the results of the study can readily be generalised to the wider patient population.

Randomisation will be implemented and administered using a secure web-based service at the clinical trial unit (CTU) at Warwick Medical School (University of Warwick). A minimization algorithm (sometimes referred to as adaptive randomization) will be used to randomise study participants; at recruitment of each new study participant this algorithm attempts to balance the marginal totals for each level of the stratification factors (**age** and **recruiting centre**). This is the usual practice for trials run at Warwick CTU. Experience indicates that for studies where some centres recruit only a relative small number of patients this method tends to perform better than conventional stratification methods.

Randomisation will be on a 1:1 basis to either **intramedullary nailing** or **'locking'-plate fixation**. Both of these operations are widely used within the NHS and all of the surgeons in the chosen centres will be familiar with both techniques.

Baseline demographic data, radiographs and pre-injury functional data using the DRI and the Olerud and Molander Questionnaire will be collected. The patients will also be asked to fill out the EuroQol EQ-5D health-related quality of life questionnaire to indicate their typical pre-injury health status.

A research associate will perform a clinical assessment and make a record of any early complications at 6 weeks and a radiograph will be taken. A further clinical assessment and radiograph will also be taken at 12 months post-operatively to detect late complications. Functional outcome, health-related quality of life and resource use questionnaires will be collected by post at 3 months, 6 months and 12 months post-operatively.

A total sample size of 264 patients represents the most likely scenario, based on our current knowledge, assuming DRI is approximately normally distributed, the standard deviation is 20 points and a clinically important difference of 8 points, with power set at 90% and significance at 5%. Allowing a margin of 20% loss during follow-up, this gives a figure of **320 patients in total**. Therefore, **160 patients randomized to each group** will provide 90% power to detect a difference of 8 points in DRI at 6 months with 90% power at the 5% level.

4.2 Objectives

The **primary objective** is:

To quantify and draw inferences on observed differences in the Disability Rating Index (DRI) between the trial treatment groups at 6 months after injury.

The **secondary objectives** are:

1. To quantify and draw inferences on observed differences in early functional status (measured by the DRI) at 3 months and later functional status at 12 months.
2. To quantify and draw inferences on observed differences in the radiological outcomes: nonunion, mal-alignment and shortening.

3. To identify any differences in health-related quality of life between the trial treatment groups in the first year after the injury.

4. To determine the complication rate of intramedullary nail fixation versus 'locking'-plate fixation in the first year after the injury.

5. To investigate, using appropriate statistical and economic analytical methods, the resource use, costs and comparative cost effectiveness of intramedullary nail fixation versus 'locking'- plate fixation.

4.3 Outcome measures

Table 1: Summary of outcome measures to be collected at each time point

Baseline	DRI OMAS, EQ-5D *pre-injury*, *EQ-5D current health status 'as of today'*, & radiographs
6 weeks	Complication records, radiographs and operative record
3 months	DRI, OMAS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire
6 months	**DRI (primary outcome)**, OMAS, EQ-5D, record of complications/rehabilitation or other interventions and resource use questionnaire
12 months	DRI, OMAS, EQ-5D, radiographs, record of complications/rehabilitation or other interventions and resource use questionnaire
Annual	Postal DRI, EQ-D5 and further treatment questionnaire (recording any post-operative Questionnaire problems or treatments)

The **primary outcome measure** for this study is the **Disability Rating Index (DRI)**. The DRI score is a validated questionnaire which is self-reported (filled out by the patient). It consists of 12 items specifically related to function of the lower limb. This data will be collected at baseline, 3, 6 and 12 months post-operatively. The DRI has been proven to be a robust and practical clinical research instrument with good responsiveness and acceptability for assessment of disability caused by impairment in the lower limb.

The **secondary outcome measures** in this trial are:

Olerud and Molander Score (OMAS): This is a self-administered patient questionnaire. It is a good outcome tool for assessing symptoms after an ankle fracture. The score is based on nine different items: pain, stiffness, swelling, stair climbing, running, jumping,

squatting, supports and work/activities of daily living. The scoring system correlates well with parameters considered to summarise the results after this type of injury and is therefore recommended for use in scientific investigations.

EQ-5D (3L): The EQ-5D is a validated, generic health-related quality of life measure consisting of 5 dimensions each with a 3-level answer possibility. Each combination of answers can be converted into a health utility score. It has good test-retest reliability, is simple for patients to use, and gives a single preference-based index value for health status that can be used for broader cost-effectiveness comparative purposes.

Complications: All complications will be recorded, including malunion, delayed/non-union, infection, wound complications, vascular and neurological injury and venous thrombo-emboism. A record will also be kept of any other surgery required in relation to the index fracture, including removal of any metalwork.

Radiographic evaluation: Standard anterior-posterior and lateral radiographs of the tibia and fibula will be taken at baseline, 6-weeks and 12 months after the injury. These radiographs are those routinely used for the investigation of patients with a suspected fracture of the distal tibia and for the follow-up of such patients following any intervention, so there will be no need to request any additional or special investigations.

5. DATA MONITORING

The Case Report Forms (CRFs) will be designed by the trial coordinator in conjunction with the trial management team. All electronic patient-identifiable information will be held on a secure, password-protected database accessible only to essential personnel. Paper forms with patient-identifiable information will be held in secure, locked filing cabinets within a restricted area of Warwick Medical School. Patients will be identified by a code number only. Direct access to source data/documents will be required for trial-related monitoring. All paper and electronic data will be retained for at least five years after completion of the trial.

Full details of management and checking of CRFs, x-rays, participant postal questionnaires and SAE forms are given in the **FixDT Data Management Plan**. For newly employed data administrators entering data the trial coordinator will perform a 100% data check of a minimum of 30 CRFs and questionnaires entered or until the error rate is less than 1%. A routine 10% check will be performed every month; the sample will be generated from the forms entered that month. If an error rate of over 1% is found, then an additional sample will be taken. If a further 1% error rate is found, then a 100% check will be performed of the particular forms concerned.

Monitoring of the trial is a continual process, from the start to the end of the trial. The objectives of the statistical input during trial monitoring are to:

- Give an overview of the recruitment and follow-up
- Examine the quality of data
- Ensure the protocol is being adhered to
- Assess the randomisation sequence
- Statistical reporting

The Trial Steering Committee (TSC) and the Independent Data Monitoring Committee (DMC) are given the responsibility of monitoring the accumulating data. Statistical reports that provide oversight on the quality of the trial will be produced to cover the below issues. There are no planned interim analyses, unless requested by the DMC.

The recruitment in the trial will be summarised regularly by the trial co-ordinator. Recruitment is continuously assessed by the trial co-ordinator, in conjunction with the statistician where appropriate, in order to check whether actual accrual is meeting projected targets, overall and by each centre.

The follow-up rates are based on postal questionnaire completion rates, and will be calculated regularly by the trial co-ordinator. Considerable efforts will be made by the trial team to keep in touch with patients throughout the trial to minimise loss to follow up. Rates will be calculated as follows:

% Follow-up rate (at time T) =

$$\frac{\text{Number of participants assessed at time } T}{\text{Total no.that should have been assessed at time } T} \times 100$$

Participants who have died before time T will not be counted in the denominator of rates. We expect a very small number of deaths during follow up. The follow-up rates will be computed at the following time-points:

- Follow-up at 3 months
- Follow-up at 6 months (primary outcome)
- Follow-up at 12 months
- Follow-up annual questionnaire, for up to 10 years

The template table (Table 4) given in Section 8: will be used to present the follow-up rates.

6. STATISTICAL ANALYSIS

6.1 Software

When any analyses are required, data will be retrieved from the trial database by the trial statistician. The statistician will import data directly into an appropriate statistical package. All analyses and reporting will be conducted using either Stata or R (http://www.r-project.org/) using an ODBC (Open DataBase Connectivity) link; the version numbers of all software used, data files and all code will made available to the Data Monitoring Committee (DMC) on request at any stage of the trial. Statistical results will be reported in accordance with CONSORT guidelines (http://www.consort-statement.org/).

6.2 Data validation

Prior to formal analysis, data will be checked for outliers, missing values and validated using the defined score ranges for all outcome measures. Queries will be reported to the trial coordinator and investigated. Standard statistical summaries (e.g. medians and ranges or means and variances, dependent on the distribution of the outcome) and graphical plots showing correlations will be presented for the primary outcome measure and all secondary outcome measures. Baseline data will be summarized to check comparability between treatment arms, and to highlight any characteristic differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

6.3 Missing data

It seems likely that some data may not be available due to voluntary withdrawal of patients, lack of completion of individual data items or general loss to follow-up. Where possible the reasons for data 'missingness' will be ascertained and reported. Although missing data are not expected to be a problem for this study, the nature and pattern of the missingness will be carefully considered — including in particular

whether data can be treated as missing completely at random (MCAR). If judged appropriate, missing data in the primary outcome (DRI) can be imputed using the ICE (imputation by chain equation) procedure in Stata (www.ats.ucla.edu/stat/stata/library/ice.htm). Any imputed data will be on an individual item level, as opposed to an overall score level. Any imputation methods used will be carefully considered and justified. Reasons for ineligibility, non-compliance, withdrawal or other protocol violations will be stated and any patterns summarized. More formal analysis, for example using logistic regression with 'protocol violation' as a response, may also be appropriate and aid interpretation.

6.4 Interim analyses

There are no pre-planned interim analysis in the FixDT trial. Interim analyses will be performed only where directed by the DMC. Interim analyses will follow the same procedure as the final analyses.

6.5 Final statistical datasets

There will be two potential datasets used for the statistical analysis: (a) Observed and (b) Imputed (Primary outcome only).

6.5.1 Feasibility Study

At the end of the feasibility phase, the overall mean recruitment rates at the six selected centres for this phase of the study will be estimated (with a 95% confidence interval based on a normal approximation) and compared to the **target rate of 0.75 patients per month per centre**. The estimated recruitment rate in the feasibility phase will inform both the design and the decision to proceed to the main RCT. Additionally the nature and pattern of trial withdrawals and the likely impact of this on the main RCT will also be carefully considered.

6.5.2 Main RCT

The primary analyses will be performed on an 'intention to treat' (ITT) basis. This involves analysing all patients within their randomised groups, regardless of whether they completed their allocated treatment.

As a sensitivity analysis, the 'Per protocol' (PP) analyses will also be performed in addition, to place the results from the ITT analysis in context. The per-protocol analyses will remove the patients who have not complied with the protocol. If non-compliance becomes a problem them the planned analysis will be augmented with a Complier Average Causal Effect (CACE) analysis, but this should not be an issue in this trial.

6.5.2.1 Randomisation

The numbers of patients randomised and screened has been detailed in Table 1. The randomisation of all eligible patients will be summarized in Tables 5 and 6, which will present:

- The number (%) of patients randomised to each treatment group at each centre
- The number (%) of patients randomised to each treatment summarized by randomisation strata at each centre

6.5.2.2 Baseline Data

The baseline demographic and clinical characteristics of all randomised patients will be summarized by treatment group in Tables 7 – 9 (CHECK)

6.5.2.3 Harm Data (SAE's)

The number (%) of SAE's will be summarized by treatment group in Tables 10 and 11. Individual number of SAE's and the number of SAE's per patient will be presented.

6.5.2.4 Non-adherence to protocol

The DMC will monitor crossovers and non-adherence and offer advice on whether modifications to analysis should be made. There will be patients who are likely not to adhere to the protocol or depart from the intended treatment and/or evaluation. Any patients that depart from the intended treatment will be referred to as having "not adhered" to protocol for the purpose of the analyses. The following list is not by any means complete and during the trial further patients who do not adhere to the protocol will be identified. Currently non-adherence to the protocol consists of:

(i) Withdrawals;

(ii) Ineligible patients: Any patients who were ineligible but were subsequently randomised into the trial;

(iii) Patients who receive an alternative treatment: Any patients who do not receive their allocated treatment (either through their own choice or as a surgical decision);

(iv) Incomplete follow up: Any patients who have no follow up data at all.

6.5.2.5 Primary Outcome

The main analysis will investigate differences in the primary outcome measure, the DRI at 6 months after surgery, between the two treatment groups on an intention-to-treat basis. In addition, early functional status will also be assessed and reported at 3 months and later functional status at 12 months. The differences between treatment groups will be assessed using a Student t-test, based on a Normal approximation for the DRI score at 6 months, and at other occasions. Tests will be two-sided and considered to provide evidence for a significant difference if p-values are less than 0.05 (5% significance level). Estimates of treatment effects will be presented with 95% confidence intervals.

The minimization procedure used for randomization will ensure approximate balance in treatment allocation across recruiting centres and age groups (<50 and 50+ years). We anticipate that any individual surgeon will operate on no more than 2-3 patients, so we do not expect surgeon-specific effects to be important in this study. However, in addition to the unadjusted analyses (t-tests) we will also undertake regression analyses to adjust for any imbalance between treatment groups in patient baseline (pre-injury) DRI, age and gender. The fixed effects analysis (linear regression model) will also be generalized by adding a random effect for recruiting centre to allow for possible heterogeneity in patient outcomes due more generally to the recruiting centre.

The mixed-effects regression will be the definitive analyses and will be undertaken using the specialist mixed-effects modelling functions available in the software package R (http://www.r-project.org/). DRI data will be assumed to be approximately normally distributed; possibly after appropriate variance-stabilising transformation. The primary focus will be the comparison of the two treatment groups of patients, and this will be reflected in the analysis which will be reported together with appropriate diagnostic plots that check the underlying model assumptions.

Results will be presented as mean differences between the trial groups, with 95% confidence intervals.

6.5.2.5 Secondary Outcomes

Secondary analyses will be undertaken using the above strategy for approximately normally distributed outcome measures OMAS and EQ-5D. For dichotomous outcome variables, such as indicators of deep infection and other complications related to the trial interventions, mixed effects logistic regression analysis will be undertaken with results presented as odds ratios (and 95% confidence intervals) between the trial groups. The temporal patterns of any complications will be presented graphically and if appropriate a time-to-event analysis (Kaplan-Meier survival analysis) will be used to assess the overall risk and risk within individual classes of complications (e.g. infection). Only a small number of patients are expected to die during follow-up, so this is unlikely to be a serious cause of bias. However, we will also if appropriate conduct a secondary analysis taking account of the competing risk of death, based on cumulative incidence functions. If multiple complications prove to be widely reported, then a secondary analysis will use a Poisson regression model to assess overall differences in counts of events between groups, adjusting for potential confounding factors such as age and gender. Multiple complications are defined as two or more independent events, i.e. not continuations of a previous complication, for the same patient and will be identified only after discussion with the clinical team.

6.6 Analysis plan

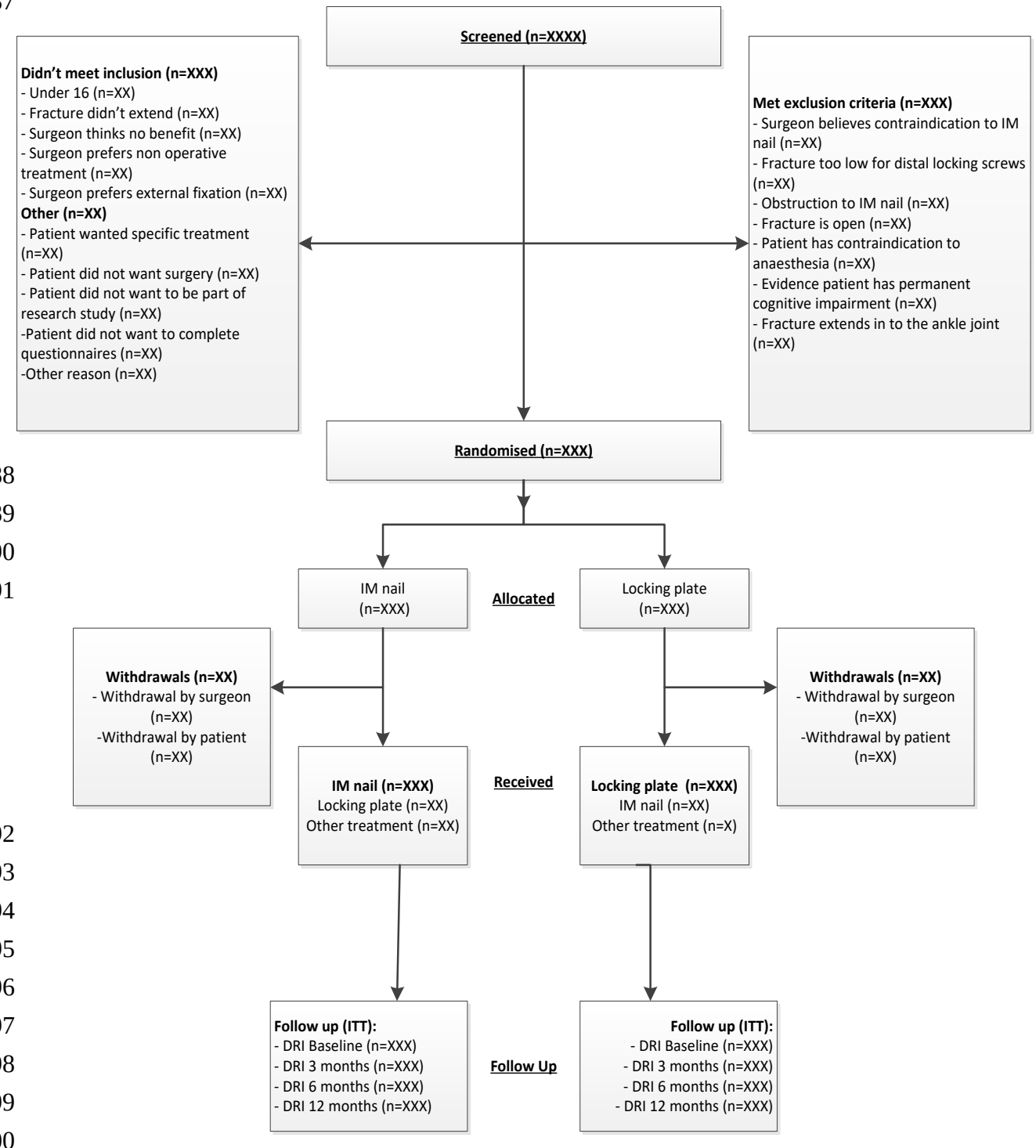
The statistical analysis plan (SAP) will be agreed with the Data management Committee (DMC) at the start of the study. Any subsequent amendments to this initial SAP will be clearly stated and justified. Interim analyses will be performed only where directed by the DMC. The routine statistical analysis will mainly be carried out using Stata.

6.7 Reporting

Wherever possible, the results of all analyses will be presented in a simple and easy to follow manner and relate any observed differences to their clinical importance, such that they could be clearly understood by those with only rudimentary statistical

knowledge. Open and confidential reports of the statistical analyses will be produced, as required, by the trial statistician and where appropriate results will be disseminated through peer-reviewed journals, conference presentations and through local mechanisms.

7. CONSORT DIAGRAM (proposed)



8. TEMPLATE TABLES

Table 1: Flow of patients in the FixDT trial

FROM SCREENING TO PRE-RANDOMISATION	All patients screened	n (%)
	Excluded Patients: Patients not meeting inclusion criteria	n (%)
	Excluded Patients: Patients meeting inclusion criteria but also meet at least one of the exclusion criteria.	n (%)
PRE-RANDOMISATION	Patients with baseline data	n (%)
RANDOMISATION	Patients satisfying the inclusion criteria and RANDOMISED	n (%)
	Patients satisfying the inclusion criteria and NOT RANDOMISED	n (%)
	Patient randomised but ineligible	n (%)
FOLLOW-UP	No follow-up data at any time point	n (%)
	Follow-up data at 3 months only	n (%)
	Follow-up data at 6 months only	n (%)
	Follow-up data at 3 and 6 months only	
	Follow-up data at 12 months only	n (%)
	Follow-up data at 3 and 12 months only	
	Follow-up data at 6 and 12 months only	
	Follow-up data at all time points	n (%)
DIED	After randomisation but before theatre for treatment	n (%)
	In theatre but before starting any procedure	n (%)
	During initial treatment in hospital	n (%)
	After hospital discharge after initial treatment but before 3 month follow-up	n (%)
	After 3 month follow-up but before 6 month follow-up	n (%)
	After 6 month follow-up but before 6	n (%)

	month follow-up	
WITHDRAWALS	After randomisation but before treatment	n (%)
	After treatment commencement but before 6 month follow-up	n (%)
	After 6 month follow-up but before 12 month follow-up	n (%)

Table 2: Withdrawal details summarised by treatment group

		IM Nail	**Locking plate**	**TOTAL**	**P-value**
Patient requested to withdraw from trial	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Surgeon caring for patient requested for patient to be withdrawn	Yes	n (%)	n (%)	N	xx.xx
	No	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Patient level of withdrawal	Not stated	n (%)	n (%)	N	xx.xx
	Withdrawn from completing further questionnaires, but allowed trial team access to future hospital data (including x-rays)	n (%)	n (%)	N	
	Withdrawn wholly from the study, and only data obtained up to withdrawal date included in any analysis.	n (%)	n (%)	N	

Listing 1: If patient expressed wish to withdraw and reason known, please specify reason below

Listing of reasons will be by treatment group. The following will be listed: Patient number, centre, timing of withdrawal and reason for withdrawal.

Listing 2: If surgeon caring for patient requested for the patient to be withdrawn, please specify reason below

Listing of reasons will be by treatment group. The following will be listed: Patient number, centre, surgeon name, timing of withdrawal and reason for withdrawal.

Table 3: Patients who did not receive allocated treatment summarised by treatment group

		PHT	HA	TOTAL	P-value
If patient did not receive allocated treatment, what treatment did they receive	IM nail	n (%)	n (%)	N	xx.xx
	Locking plate	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Reason why IM nail not used if patient allocated to IM nail	???	n (%)	n (%)	N	xx.xx
	???	n (%)	n (%)	N	
	???	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	
Reason why locking plate not used if patient allocated to locking plate	???	n (%)	n (%)	N	xx.xx
	???	n (%)	n (%)	N	
	???	n (%)	n (%)	N	
	Other	n (%)	n (%)	N	
	Missing	n (%)	n (%)	N	

Listing 3: If patient did not receive allocated treatment and received 'Other' treatment, please specify

Listing of 'other' treatment received will be by allocated treatment group. The following will be listed: Patient number, centre and specification of 'other' treatment given.

Table 4: Follow-up rates in the FixDT Trial

	3 Months	6 Months	12 Months
Completed questionnaire	n (%)	n (%)	n (%)
Awaiting questionnaire	n (%)	n (%)	n (%)
No reply (after full chasing)	n (%)	n (%)	n (%)

No contact/being chased	n (%)	n (%)	n (%)
Consent withdrawn	n (%)	n (%)	n (%)
Dead	n (%)	n (%)	n (%)

Table 5: Randomised patients summarised by treatment group and centre

	IM Nail	Locking plate	TOTAL
UHCW, Coventry	n (%)	n (%)	N
Frenchay Hospital, Bristol	n (%)	n (%)	N
University Hospital Leicester	n (%)	n (%)	N
James Cook Hospital, Middlesbrough	n (%)	n (%)	N
⋮	⋮	⋮	⋮

Table 6: Randomised patients summarised by randomisation strata (recruiting site, age and FAI type)

Age:	**Age <50**		**Age >= 50**	
	IM Nail	**Locking plate**	**IM Nail**	**Locking plate**
UHCW, Coventry	n (%)	n (%)	n (%)	n (%)
Frenchay Hospital, Bristol	n (%)	n (%)	n (%)	n (%)
University Hospital Leicester	n (%)	n (%)	n (%)	n (%)
James Cook, Middlesbrough	n (%)	n (%)	n (%)	n (%)
⋮	⋮	⋮	⋮	⋮

Table 7: Baseline demographic and clinical characteristics of all randomised patients summarised by treatment group

		IM Nail	Locking Plate	TOTAL
Age (years)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Side of fracture	Left	n (%)	n (%)	N
	Right	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Mechanism of injury	Low energy fall	n (%)	n (%)	N
	High energy fall	n (%)	n (%)	N
	Road traffic accident	n (%)	n (%)	N
	Crush injury	n (%)	n (%)	N
	Contact sports injury	n (%)	n (%)	N
	Other	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Height (cm)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Weight (kg)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx

	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Current smoking status	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
If yes, for how many years smoking	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
If yes, how many smoked on average per day	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Units of alcohol in an average week	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
Diabetes status	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Previous problems with the lower limb on the injured side?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Disability Rating	Mean	xx.xx	xx.xx	xx.xx

Index (Baseline)	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D Mobility (Pre-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Self-care (Pre-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Usual activities (Pre-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Pain/discomfort (Pre-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Anxiety/depression (Pre-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Score (Pre-injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D VAS (Pre-injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx

	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D Mobility (Post-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Self-care (Post-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Usual activities (Post-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Pain/discomfort (Post-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Anxiety/depression (Post-injury)	Level 1	n (%)	n (%)	n (%)
	Level 2	n (%)	n (%)	n (%)
	Level 3	n (%)	n (%)	n (%)
	Missing	n (%)	n (%)	n (%)
EQ-5D Score (Post-injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx
EQ-5D VAS (Post-injury)	Mean	xx.xx	xx.xx	xx.xx
	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx

	Missing	xx.xx	xx.xx	xx.xx

Table 9: Operation notes summarised by treatment group

		IM Nail	Locking Plate	TOTAL
Any intra-operative problems?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
If yes, any nerve injury?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
If yes, any vascular injury?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
If yes, any tendon injury?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
If yes, any extension of fracture?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
Which fixation method was performed?	IM nail	n (%)	n (%)	N
	Plate	n (%)	n (%)	N
	Other	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
Was this different to randomisation?	Yes	n (%)	n (%)	N
	No	n (%)	n (%)	N
	Missing	n (%)	n (%)	N
<u>If IM nail used</u>:		n (%)		
How many bolts were used in coronal plane?	0	n (%)		
	1	n (%)		
	2	n (%)		
	Missing	n (%)		
How many bolts were used in sagittal plane?	0	n (%)		
	1	n (%)		

	2	n (%)		
	Missing	n (%)		
How many bolts were used in oblique plane?	0	n (%)		
	1	n (%)		
	2	n (%)		
	Missing	n (%)		
How many blocking screws were used?	0	n (%)		
	1	n (%)		
	2	n (%)		
	3	n (%)		
	4	n (%)		
	Missing	n (%)		
What reduction technique was used for the nail?	Open	n (%)		
	Closed	n (%)		
	Skeletal traction	n (%)		
	No traction	n (%)		
	Missing	n (%)		
What surgical approach was used?	Medial parapatella	n (%)		
	Lateral parepatella	n (%)		
	Tendon splitting	n (%)		
	Suprapatella approach	n (%)		
	Missing	n (%)		
<u>If locking plate was used:</u>				
How many screws were used distal to the fracture?	1		n (%)	
	2		n (%)	
	3		n (%)	
	4		n (%)	
	5		n (%)	
	6		n (%)	
	6+		n (%)	
	Missing		n (%)	
How many screws were	0		n (%)	

used proximal to the fracture?	1		n (%)	
	2		n (%)	
	3		n (%)	
	4		n (%)	
	5		n (%)	
	5+		n (%)	
	Missing		n (%)	
More to add here…				

680

681 **Table 10: Serious Adverse Events (SAE's) summarised by treatment group**

Reason	IM Nail	Locking Plate	TOTAL
Death within 30 days of trial treatment	n (%)	n (%)	N
Death related to the trial surgical intervention at any time	n (%)	n (%)	N
A life or limb threatening complication	n (%)	n (%)	N
Prolongation of existing hospitalisation	n (%)	n (%)	N
Re-hospitalisation for any leg treatment (trial leg)	n (%)	n (%)	N
Other medically significant reason for reporting	n (%)	n (%)	N
Missing	n (%)	n (%)	N

682

683 Could expand these further?

684

685 **Table 11: Principal Investigator's assessment of SAE's summarised by treatment group**

	IM Nail	Locking Plate	TOTAL
Expected	n (%)	n (%)	N
Unexpected	n (%)	n (%)	N
SAE caused by taking part in FixDT	n (%)	n (%)	N
SAE not caused by taking part in FixDT	n (%)	n (%)	N
Missing	n (%)	n (%)	N

686

687 **Listing 4: If SAE caused by taking part in the FixDT trial, please specify**

688 Listing will be by treatment group. The following will be listed: patient number, person making
689 judgement and date

690

691 **Table 12: Primary outcome at 6 months summarised as a continuous outcome by treatment group**

		IM Nail	Locking Plate	TOTAL
Disability Rating Index (DRI)	Mean	xx.xx	xx.xx	xx.xx

	N	xx.xx	xx.xx	xx.xx
	Std. Deviation	xx.xx	xx.xx	xx.xx
	Median	xx.xx	xx.xx	xx.xx
	Minimum	xx.xx	xx.xx	xx.xx
	Maximum	xx.xx	xx.xx	xx.xx
	Missing	xx.xx	xx.xx	xx.xx

692

693 **Figure 2: Observed treatment difference plot with 95% confidence interval**

694

695 **Table 13: Secondary outcomes at follow-up (3, 6, and 12 months) summarised by treatment group**

			IM Nail	Locking Plate	TOTAL	P-value
Disability Rating Index (DRI)	**3 months**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	12 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
Olerud-Molander Ankle Score (OMAS)	**3 months**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	

		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	12 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
EQ-5D (Mobility)	**3 months**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	12 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Self care)	**3 months**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	12 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Usual activities)	**3 months**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	

		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	12 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Pain/discomfort)	**3 months**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	12 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D (Anxiety/depression)	**3 months**	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	6 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
	12 months	Level 1	n (%)	n (%)	n (%)	xx.xx
		Level 2	n (%)	n (%)	n (%)	
		Level 3	n (%)	n (%)	n (%)	
		Missing	n (%)	n (%)	n (%)	
EQ-5D Score	**3 months**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	

		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	12 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
EQ-5D VAS	**3 months**	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	6 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	
		Missing	xx.xx	xx.xx	xx.xx	
	12 months	Mean	xx.xx	xx.xx	xx.xx	xx.xx
		N	xx.xx	xx.xx	xx.xx	
		Std. Deviation	xx.xx	xx.xx	xx.xx	
		Median	xx.xx	xx.xx	xx.xx	
		Minimum	xx.xx	xx.xx	xx.xx	
		Maximum	xx.xx	xx.xx	xx.xx	

		Missing	xx.xx	xx.xx	xx.xx	

Still to do: add process variables table.

9. AMENDMENTS