Changes to protocol version 1.7 creating version 1.9 1st April 2014 (the changes made from version 1.7 to 1.8 12 March 2014 are as outlined below except that it was planned that adherence questionnaires would be done once a year during the long term follow up. It was subsequently decided that adherence questionnaires should be done every 12-16 weeks and acceptability questionnaires at re-starting continuous ART or at the end of the study. It was also decided that a CRF should be completed every 12-16 weeks rather than once a year during the long term follow up, and that tanner scales and routine FBC and biochemistry results did not need to be collected. Flowsheet 1.13, section 8.10 and the new information sheets and consent forms in appendices 17-20 were updated to reflect this. Version 1.8 was approved by the Irish Medicines Board before this update was made, but not reviewed or approved in the other countries)

Major changes:

General Information, Abbreviations, sections 3.2, 10.4, 15, appendix 16: The MRC CTU became part of UCL on 1st August 2013. All MRC CTU employees are now employed by UCL and UCL is responsible for providing indemnity for sites in the UK.

General Information, Abbreviations, section 3.2, 10.3, appendix 16: INSERM-SC10 became INSERM SC10-US019

Section 1.6, 1.7.2, 7.12, 8.11.1, appendix 12: End of trial definition changed from once last participant enrolled has been followed for 48 weeks (now defined as completion of main trial) to once all participants have had their final long term follow up visits

Section 1.6, 1.13, 4.1, 8, 8.10, 8.11.1, appendix 15: The TSC recommended that participants are followed for 2 years after completion of the main trial (long term follow up). A flowsheet has been generated for this long term follow up including completion of adherence questionnaires every 12-16 weeks, completion of acceptability questionnaires at re-starting continuous ART or at the end of the study, and storage of a plasma sample at the final visit for future HIV-related tests

Section 1.6, 1.13, 7.12, 8.10, appendix 15: Management of HIV-1 RNA viral load should continue as specified in appendix 15 if the participant continues follow up in the trial after the main trial is completed

Section 7.12, appendix 12: The TSC recommended that young people be allowed to stay on SCT between the main trial completion and publication of the results provided that they are virologically suppressed, the clinician and family agree, and 12-16 weekly viral load monitoring can be performed

Appendices 17-20: New information sheets added for long term follow up in SCT (appendix 17) and CT (appendix 19) arms for parents/carers, young adults, young people, children and children taking medicines long term (unaware of diagnosis), and new consent forms for parents/carers and young adults and assent forms for young people/children for SCT (appendix 18) and CT (appendix 20) arms

Minor changes:

General Information: Clarification that funding by PENTA from current EU grant is available until 2015
General information, section 3.2: Updates made to participating centres and MRC CTU contact details
Sections 2.6, 8.1, 8.4, 8.11.2, 10.3, appendix 11: minor clarifications to text
Section 10.1, 10.2: Clarification that pregnancies are notable events and should be reported on an SAE form, and that if a participant on the SCT becomes pregnant they should return to CT
Section 8.10, 10.2: Safety reporting to continue as per protocol for entire duration of follow up within the trial
Appendix 11: Proviral DNA will not be quantified in young people in the pilot phase of the SCT arm at weeks 1, 2, and 3 as PBMCs are required for this but only plasma was collected at these visits. Low level viral loads will be done to <10 c/ml rather than <3 c/ml as this is what is currently feasible
Appendix 12 – qualitative sub study consent forms – clarification that there will be 2-3 interviews (rather than just two)
Appendix 16: Other updates to contact details (non-MRC CTU)

Changes to protocol version 1.6 creating version 1.7 24 April 2013

Major changes:

Sections 1.3, 1.8, 4.1, 5.5, 11.3, Appendix 1, Appendix 3: Sample size updated to a minimum of 160 participants

The TSC and IDMC supported a proposal to enrol as many young people as possible in the time available, even if this exceeds 160. They agreed that this would enhance the power of the study and allow continuing collaboration with new centres.

Section 1.6, 4.1: Recruitment period updated to 27 months, i.e. up until end of June 2013

Section 11.3: Justification for updating sample size to a minimum of 160 and a maximum of 220 participants added

Section 2.6, 8.5, 13.2: Minor re-wording to clarify that not all resistance tests will need to be done centrally and may be performed locally where feasible.

Appendix 11: Clarification that resistance testing will be performed locally and that if this is not possible, or the amino acid sequence cannot be provided in a FASTA file format, they will be performed centrally.

The TMG agreed that centralised viral load testing on samples ≥50 c/ml would introduce non-random bias and that the variation between assays that exists in reality should not systematically bias randomised comparisons.

Section 11.4: Stopping criteria updated

Appendix 12: Inclusion of data collection with non-trial participants; focus groups with non-trial participants and interviews with carers. These and the associated information sheets and consent forms will have ethical approval sought from LSHTM)

Minor changes:

Section 1.6: Clarification that the end of trial will be once the last participant randomised has completed 48 weeks of follow-up.

Section 1.7.3: Minor re-wording

Section 1.8: Clarification that participants that have completed 48 weeks of follow-up will be seen every 12 weeks thereafter until the end of the trial.

Section 4.3: A scan of the original CRF may be sent to the Trials Unit for data entry for some centres

Section 5.5: There will be single centre in the Ukraine, therefore wording updated

Section 6.1.2: Clarification that RA/RO phenotypes to be collected if available

Section 7.5.2: Minor re-wording

Section 11.1: Update to 24 years for 18-21 year age strata (not updated in protocol version 1.6 in error)

Section 11.4: Updated wording regarding IDMC review of pilot and outcome

Section 18: Clarification in Changes to protocol version 1.5 creating version 1.6 29 June 2012 that the Qualitative Substudy information sheets were updated as described (and not the main trial information sheets)

Appendix 12: Clarifications that Dr Sarah Bernays will also be managing the qualitative study, trial participants must be aged 10-24 year olds, three interviews will be conducted where feasible, exploring participants' interest in contributing an audio diary in the latter half of the trial will not necessarily need to be at around 36 weeks, focus groups will be conducted in Uganda (with trial participants), incentives will not be provided for focus groups but food and refreshments will be provided and travel costs reimbursed

Appendix 15: Clarifications added to flow chart for managing viral loads regarding viral load results reported as <XX c/ml where XX>50

Appendix 16: Marc Lallemant changed to Tim Cressey in TMG. Anna Turkova added to TMG.

Changes to protocol version 1.5 creating version 1.6 29 June 2012

Major changes:

Abbreviations and Glossary, sections 1.3, 2.5, 5.1, 9.2, Appendix 12 Qualitative Substudy information sheets for parents/carers, young adults and young people: Upper age limit for young person/people eligible for trial entry increased to 24 years of age

Sections 1.6 and 4.1: Recruitment period updated to 24 months in total

Appendix 12: Addition of USA to Qualitative Substudy

Minor changes:

General Information, sections 3.2, 5.5, Appendix 14 and Appendix 16: Participating centres updated

Sections 4.2 and 11.6: Correction of typing error – young people with a HIV-1 RNA ≥50 copies/ml at week 8 (pilot phase only) must have a repeat test on a separate sample within 1 week

Appendix 15: Clarification that participants in the CT arm should have a repeat VL on a separate sample within 1 week if any VL ≥ 50. Clarification that if a participant enrolled to the pilot phase had a confirmed blip at any of weeks 1, 2 or 3 in the pilot phase, then they would need to return to CT if they have 2 unconfirmed blips in the main phase of the trial.

Changes to protocol version 1.4 creating version 1.5 19th December 2011

Major changes:

Text relating to the pilot phase only now appears in grey; including in the flow charts 1.09, 1.10 and Appendix 15, and has been removed in the Sample Patient Information Sheets (Appendix 1).

Section 2.6 Risks and benefits: The statement 'Safety in the pilot study will be assured before moving to the main trial' has been replaced with 'Data from the pilot phase has been reviewed by the IDMC who identified no safety concerns and recommended that recruitment continue'. This statement has also been added to the Patient Information Sheets in Appendix 1.

Section 6.1.1 Enrolment and consent: Minor re-wording of text removing reference to pilot.

The requirement for local HIV-1 RNA viral load measurement at randomisation (week 0) has been removed affecting: flowsheets in section 1.11 and 1.12, and section 6.2.

Screening visit (section 6.1.2): Previously stated screening should take place no more than four weeks prior to randomisation (week 0) and ideally two weeks before. This has been changed to state that randomisation (week 0) should take place no more than

four weeks after screening and ideally as soon as possible after eligibility has been confirmed. This change is also reflected in section 7.3.

For young people randomised to SCT, a comment has been added in sections 1.2, 4.1 and 7.3 to state that if alternative consecutive days to Saturday-Sunday or Friday-Saturday are taken off ART to better suit a particular young person's normal routine then the days should be decided at enrolment and remain constant throughout the study period. This has also been added to the Patient Information Sheets in Appendix 1 stating that young people/parents/carers should discuss this with their nurse/doctor prior to enrolment.

Changes to the inclusion and exclusion criteria (affecting sections 5.1 and 5.2):
Participants can be on a regimen containing NtRTIs (i.e. 2 NRTIs/NtRTIs and EFV). This has been clarified in sections 1.3, 1.8, 5.1, and 7.8.
Previously, young people who had experienced a single viral load >50 but <400 copies/ml in the last 12 months could be enrolled. This has been changed to state that young people who have experienced a single viral load >50 but <1000 copies/ml in the last 12 months can be enrolled (provided at least 3 measurements <50 copies/ml are available from the last 12 months, including screening).
Participants are no longer required to have started HAART naïve. Previous dual therapy and/or substitution of NRTIs is allowed providing any changes were not for disease progression, immunological or virological failure. The definition of virological failure has been clarified. Previous ART monotherapy (except for the prevention of mother-to-child transmission) has specifically been added as an exclusion criterion.

Appendix 1 – An information sheet for children unaware of their diagnosis has been added
The role of the Research Ethics committee has been modified in the parents/carers, young adult, and young people information sheets to state that their task is to check the study and make sure as far as possible; no harm comes to anyone from being part of the study.

Appendix 2 – Sample Consent Forms: Statement regarding use of anonymised blood samples in consent forms for parent/carers and young adults has been amended to state that they will only be used for ethically approved studies. Assent form for children unaware of diagnosis added

Appendix 5 – Acceptability questionnaire for carers – Weekends off group – Restarting continuous ART or at end of study: Question 5 reworded into two parts (a and b) to ask about the difference for the child before and after the weekend. Question 6 reworded into two parts (a and b) to ask about the difference for the carer before and after the weekend.
Acceptability questionnaire for young people – Weekends off group – Restarting continuous ART or at the end of study: Additional question introduced at beginning to ask who gives the young person their medicines (for consistency with the other questionnaires). Question 3 reworded into two parts (a and b) to ask about the difference for the young person before and after the weekend. Additional question introduced after this (now Q4) to ask about difference before and after the study.

Appendix 12 - Qualitative Substudy – Patient Information Sheets - Wording regarding timing of interviews modified; first interview to take place in early stages of the trial and second to take place towards the end of the trial. Clarification that a third interview may be conducted if feasible and that travel expenses to attend interviews will be reimbursed.
A witness signature section has been added to all the consent forms relating to this substudy in the case that the participant/carer is unable to sign and uses a thumbprint.

Minor changes:

Minor re-wording for clarification: general information; 1.6; 1.7.3; 5.1; 6.1.1; 6.2; Appendix 11
Updates to contact details: general information; Appendix 16

Changes to protocol version 1.3 creating version 1.4 21st January 2010

Major changes:

Prof. Ian Weller, Chair of BREATHER Steering Committee added to authorisation of protocol.
Compliance and funder details changed
Section 1.2, 1.5, 1.8, 1.9 -1.12, 4.1, 4.2, 7.1, 7.2, 7.6 PIS: Addition of viral load measurements and blood stores at weeks 1, 2, 3 and 8 for participants randomised to continuous ART in the pilot phase
Section 1.9-1.12, 8.5: Reduction of timepoints for cell storage

Section 4.2, 11.6: clarification of main trial primary outcome measures for participants enrolled in the pilot phase

Minor changes and corrections:

General information: Reference to EuroCoord added
Flowsheet 1.10: Flowsheet for CT Participants in the Pilot phase added
Appendix 2: Minor re-wording of the consent forms
Appendix 16: IDMC membership added

Changes to protocol version 1.1 creating version 1.3 8th December 2010.

Note: This protocol is named version 1.3 8th December 2010 to avoid confusion with protocol version 1.2 dated 12th August 2010 which was submitted to the Thai Research Ethics Committee in error.

Major changes:

General information: committee membership and medical experts moved to Appendix 16
Section 1.9, 1.10, 1.11: Tanner stage examination moved from screening to randomisation visit. Calcium and phosphate now only at baseline and annually thereafter. Biochemistry to be carried out as per local practice.
Section 3.2, Uganda and Romania added to list of participating countries.

Section 5.2 : additions to exclusion criteria: creatinine, AST or ALT of grade 3 or above at screening; NVP or boosted PI regimen.
Section 5.3, specified that siblings can be allocated into the same arm.
Section 7.3, clarification that participants in pilot can change days off from Saturday/Sunday to Friday/Saturday, after the pilot if they wish; removal of specification that morning ART must be not be taken.
Section 8.2, collection of ethnic origin justified and reference [39] added.
Section 8.7: clarification of use of diary to provide information on adherence.
Appendix 1: Deletion of reference to text-back; clarification of where information is country/substudy specific.
Appendix 2: Addition of consent to receiving text messages, where possible.
Appendix 4 and 5. Adherence and Acceptability questionnaires revised.
Appendix 7. An alternative design for the participant diary added.
Appendix 9. Toxicity grading tables updated with August 2009 revision.

Contacts and references updated.

Minor changes made for clarification; Page 1, Sections 1.2, 1.3, 1.5, 1.9, 1.10, 1.11, 2.2.1, 2.4, 5.1, 5.2, 6.2.1, 7.1, 8, 8.2, 8.4, 8.5, 8.7, 8.8, 8.10.1, 10.4, 11.4, Appendices 14 and 15.

Changes to protocol version 1.0 creating **version 1.1 12th April 2010:**

Major changes:

1) Viral load cut off of 10,000 taken out of section 1.8, 7.2 and patient information sheets.
2) For pilot phase, option of fri/sat off ART and the attending phlebotomy visit on a Tuesday has been taken out so that the viral load is taken before recommencing ART (i.e Sat/sun off ART, viral load taken on Monday before ART recommences).
3) Clarification of how the young people in the pilot phase will be handled in terms of the primary outcome.
4) Week 1 phlebotomy visit in main trial taken out (flowsheet 1.10 amended)

5) Centralised viral loads to be measured at end of trial (section 8.5 and appendix 11).
6) Change of lipodystrophy assessment from screening visits to week 0 (flowsheets 1.9-1.11, section 8.2).

Changes to structure and minor changes to text:

7) Text about pilot phase and main trial specific requirements taken out of sections, 1.8, 4.2, 4.3, 6.2.2 and 6.2.3 and added to sections 1.2, 1.4, 1.5, 4.1, 4.2 and section 7 (7.1-7.5).
8) Thailand HIV-NAT to take part in adherence MEMS cap sub study (section 1.7.3).
9) Changes to wording of inclusion criteria (items 3 and 4).
10) Procedures for assessing efficacy text moved from section 8.9 to 4.3.
11) Clarification in text to sections 8.7.and 8.8 to state that both careers and participants should complete questionnaires, where applicable.
12) Clarification that week 8 visit is for the pilot phase SCT arm only, sections 1.5 and 8.5 have been amended).
13) Abbreviations and Glossary updated.
14) Contacts updated.