MRC Clinical Trials Unit | Smarter studies Global impact Better health | UCL

STOP-HCV Stratified Medicine for HepC

Stratified Treatment OPtimisation for HCV-1
STOP-HCV-1

Manual of Operations

v4.0 01-Nov-2017

EUDRACT #: **2015-005004-28**
CTA #: **19174/0370/001-0001**
MREC #: **15/EE/0435**

Written by:
Name: Emily Dennis
Role: Trial Manager
Signature:
Date: 01/11/2017

Authorised by:
Name: Graham Cooke
Role: Chief Investigator
Signature:
Date: 01/11/17

Version	Date	Author	Reason for revision
1.0	17-Feb-2016	Nafisah B. Atako and Cara Purvis	Initial
2.0	30-Jan-2017	Emily Dennis and Cara Purvis	Release of protocol v4.0
3.0	14-Jun-2017	Cara Purvis	Release of protocol v5.0
4.0	01-Nov-2017	Emily Dennis	Release of protocol v6.0

Contents

1. STOP-HCV-1 Communication and Procedures

The STOP-HCV-1 trial will be managed and coordinated by the MRC Clinical Trials Unit at UCL.

STOP-HCV-1 Coordinating Centre

MRC Clinical Trials Unit at UCL
Institute of Clinical Trials & Methodology
90 High Holborn,
London
WC1V 6LJ
UK

Email: mrcctu.stophcv1@ucl.ac.uk
STOP HCV-1 fax: +44 (0)20 7670 4817

MRC CTU at UCL Staff

Emily Dennis, Clinical Trials Manager e-mail: mrcctu.stophcv1@ucl.ac.uk
tel: +44 (0)20 7670 4660

Cara Purvis, Clinical Trials Manager e-mail: mrcctu.stophcv1@ucl.ac.uk
tel: +44 (0)20 7670 4930

Helen Ainscough, Data Manager e-mail: mrcctu.stophcv1@ucl.ac.uk
tel: +44 (0)20 7670 4652

Deborah Alawode, Data Manager e-mail: mrcctu.stophcv1@ucl.ac.uk
tel: +44 (0)20 7670 4614

Fleur Hudson, Operational Manager e-mail: mrcctu.stophcv1@ucl.ac.uk
tel: +44 (0)20 7670 4782

Emergency medical number (out-of-hours only): +44 (0)7773705678

E-mail Communication

To the extent possible, communication with investigators and staff regarding the STOP-HCV-1 trial will take place via e-mail or by telephone.

On occasions, when necessary, investigators and staff will receive hard-copy communications if electronic communication is deemed inadequate. In all cases, trial communications should be kept on file at each site in hard copy.

Secure e-mail will be used routinely to distribute randomisation confirmations, participant management items, data queries, and other study materials.

For methods of sending secure emails contact the STOP-HCV-1 Co-ordinating Centre.

Please direct all queries to the STOP-HCV-1 Co-ordinating Centre at the MRC CTU at UCL in the first instance using mrcctu.stophcv1@ucl.ac.uk; clinical queries will be passed to the Chief Investigator via the study team.

Randomisations

RANDOMISATIONS
To randomise, please securely email mrcctu.stophcv1@ucl.ac.uk or call MRC CTU at UCL
RANDOMISATIONS SHOULD ONLY OCCUR ON DAYS WHEN SUBSEQUENT DAY 3 VISITS CAN BE SCHEDULED IN CLINIC
Randomisation times 09:00 – 17:00
(Further randomisation information provided in section 9)

Submitting study Case Report Forms (CRFs)

It is best practice (where possible) for CRFs completed for a visit or event, to be reviewed by a second person for completeness and accuracy, before submission.

Complete the STOP-HCV-1 CRF Transmittal Cover Sheet as a record of what is being sent; instructions for completing this cover sheet are in this manual in the data collection overview. The cover sheet is available in your Investigator Site File for copying (see figure 2, section 5.4). **The original CRF that has been written on should be retained at the site.**

Securely email the STOP-HCV-1 Transmittal Cover Sheet **and** the completed CRFs to mrcctu.stophcv1@ucl.ac.uk; alternatively fax to +44 (0)20 7670 4817.

Reporting Serious Events

Detailed instructions for reporting serious events are found in Section 21 of this Manual.

Fax or secure email all SAE CRFs to the STOP-HCV-1 team at **+44 (0)20 7670 4817 or** mrcctu.stophcv1@ucl.ac.uk **within 24 hours of site awareness of the event.**

All forms must be submitted with the STOP HCV-1 CRF Transmittal Cover Sheet.

When a Serious Adverse Event is received an **email acknowledgment** will be sent to the site. If this acknowledgement has not been received within **1 working day** please contact the STOP-HCV-1 team immediately.

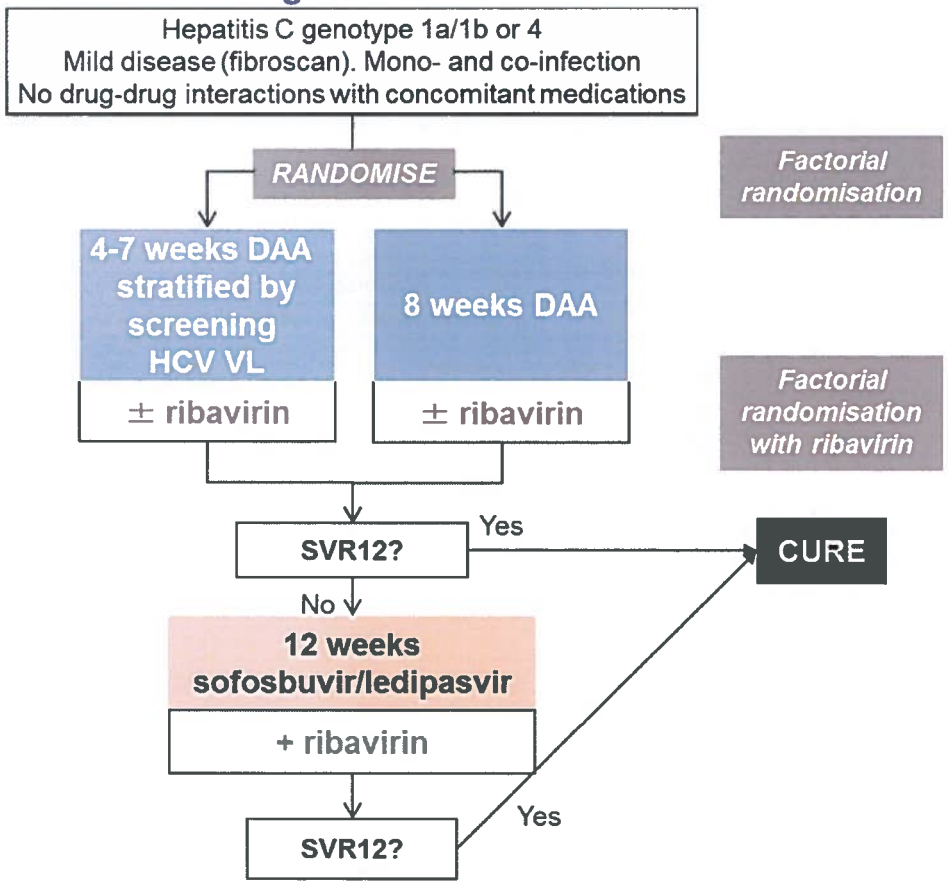
2. Trial Summary

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
Acronym	STOP-HCV-1
Long Title of Trial	**Error! Reference source not found.**
Version	6.0
Date	17-Aug-2017
ISRCTN #	ISRCTN37915093
EudraCT #	2015-005004-28
CTA #	19174/0370/001-0001
MREC #	15/EE/0435
Study Design	An open-label randomised controlled trial (RCT) testing biomarker-stratified short-course first-line and re-treatment direct-acting antiviral (DAA) oral treatment regimens to cure mild chronic Hepatitis C (HCV) disease.
Type of Patients to be Studied	Adults (≥18 years) infected with HCV genotype 1a/1b or 4 for ≥6 months, with detectable plasma HCV RNA and mild liver disease (Fibroscan score F0-F1 or biopsy proven minimal fibrosis), HCV viral load <10 million IU/ml, no previous DAA exposure (previous pegylated-interferon/ribavirin allowed) and not pregnant. Patients co-infected with HIV are eligible if HIV viral load has been <50 copies/ml for >24 weeks on anti-HIV drugs.
Setting	NHS
Interventions to be Compared	The main intervention to be compared is varying (intervention) 4-7 weeks vs fixed (control) 8 weeks combination first-line DAA treatment, with or without ribavirin, in an open-label factorial design. • Varying intervention duration will be stratified by baseline HCV RNA on a sliding scale, with duration determined by estimated time for HCV RNA to decline to reduce levels to ~1 copy in the whole body at end of treatment. • As soon as viral failure is detected at any time post-randomisation (first-line failure), patients will stop first-line treatment (if still receiving it) and be immediately retreated with 12 weeks of a different regimen. • Ribavirin will be dosed twice daily, adjusted for weight Current first-line combination regimens are those licenced for use against Hepatitis C, namely: (i) a fixed dose combination of DAA active against genotype 1a/1b and 4; the Abbvie combination ombitasvir/paritaprevir/ritonavir (12.5mg/75mg/50mg) co-formulated film-coated tablets once daily (total daily dosage:

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	25/150/100mg) plus for genotype 1a/1b one dasabuvir 250 mg tablet twice daily (total daily dosage: 500mg) (using "ombitasvir/paritaprevir/(dasabuvir)/ritonavir" to denote the combination regimen) (ii) a fixed dose combination of 2 novel DAA active against all genotypes; the Abbvie combination glecaprevir/pibrentasvir (100mg/40mg) co-formulated tablets once daily (total daily dosage: 300/120mg) Current retreatment regimens are: (iii) a fixed dose double combination of sofosbuvir/ledipasvir (400mg/90mg) once a day plus ribavirin twice a day
Study Hypotheses	**(i)** HCV-RNA determined short-course (4-7 weeks) first-line will cure similar proportions with chronic, mild HCV disease as a fixed 8 week first-line course once failures have been retreated for 12 weeks (ii) Adjunctive ribavirin improves cure rates with biomarker-stratified short-course and fixed duration DAA first-line regimens (iii) Re-treatment with a longer 12 week regimen, given after detecting virological failure on or following first-line treatment, still achieve cures in the majority of the small proportion of patients failing first-line treatment.
Primary Outcome Measure	For the varying duration comparison the primary outcome will be: ▪ Sustained Virological Response (SVR, plasma HCV RNA persistently <LLOQ (lower limit of quantification)) measured 12 weeks after the end of the combined first and any re-treatment phases (SVR12) For the ribavirin comparison the primary outcome will be: ▪ SVR12 after first-line treatment only
Secondary Outcome Measure(s)	▪ SVR12 after first-line treatment (where not the primary outcome) ▪ SVR12 after the end of the combined first and any re-treatment phases (where not the primary outcome) ▪ SVR24 after the end of the combined first and any re-treatment phases ▪ SVR24 after first-line treatment only ▪ lack of initial virological response ▪ viral load rebound after becoming undetectable ▪ serious adverse events ▪ grade 3/4 adverse events ▪ grade 3/4 adverse events judged definitely/probably related to interventions ▪ treatment-modifying adverse events (any grade) ▪ grade 3/4 anaemia ▪ emergence of resistance-associated HCV variants ▪ sensitivity/specificity of point–of-care diagnostic for IL28 ▪ costs and cost-effectiveness
Randomisation	Patients will be allocated 1:1 using a factorial design to each of

SUMMARY INFORMATION TYPE	SUMMARY DETAILS
	• biomarker-stratified varying vs fixed duration • adjunctive ribavirin or not Randomisation will be stratified.
Number of Patients to be Studied	408
Duration	▪ Patients are planned to be recruited over 2 years ▪ Each first-line intervention will be administered for 4-8 weeks ▪ Each patient will be followed for 24 weeks post end of first-line treatment: if they fail first-line, they will receive another 12 weeks re-treatment and be followed for a further 24 weeks post end of re-treatment ▪ The overall trial duration is planned for 4 years (including start-up and close-out)
Sponsor	Imperial College London
Funder	Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership (14/02/17)
Trial Manager	Emily Dennis
Chief Investigator	Graham Cooke
MRC CTU at UCL Project Leader	Ann Sarah Walker

3. Trial Flow Diagram



Follow-up: day 3, 7, 14, 28, End of Treatment; then 4-weekly until 12 weeks post end of treatment, then at 24 weeks post end of treatment.

Primary endpoint: **SVR12 (ie cure)**

Secondary endpoints: SVR24; lack of initial virological response; viral load rebound (**relapse**) after becoming undetectable; serious adverse events; grade 3 or 4 adverse events; grade 3 or 4 adverse events judged definitely/probably related to the intervention; treatment-modifying adverse events of any grade; grade 3 or 4 anaemia; emergence of resistance-associated Hepatitis C variants

4. Trial Assessment Schedules

Table 1 Trial Assessment Schedule – first-line treatment real-time tests (see Table 2 for first-line sample storage)

		DAY POST RANDOMISATION*					EOT	WEEK POST EOT			
	SCREENING†	0	3	7	14	28		4	8	12	24
Control: 8 weeks treatment [continuing]		DAA	[DAA]	[DAA]	[DAA]	DAA		*(see retreatment schedule below for any treatment after first-line EOT)*			
Intervention maximum: 7 weeks treatment [continuing]		DAA	[DAA]	[DAA]	[DAA]	DAA					
Intervention minimum: 4 weeks treatment [continuing]		DAA	[DAA]	[DAA]	[DAA]	DAA					
Eligibility assessment	X										
Patient information sheet and consent	X										
Randomisation		X									
Clinical assessment[a]		X	X	X	X	X	X	X	X	X	X
Self-reported adherence			X	X	X	X	X				
Fibroscan or biopsy**	(X)										
Weight (kg)	X					X	X	X		X	X
Height (m)	X										
Urine pregnancy test if child-bearing potential		X				X	X			X	X
Quality of life[b]		X					X			X	
EDTA blood for haematology[c,h,i] (5ml)	(X)	X			X	X	X			X	X
Clotted blood for biochemistry[d,h,i] (5ml)	(X)	X			X	X	X			X	X
Coagulation markers (2.5ml)	(X)										
Real-time HCV viral load[h,i] (10ml)	(X)	X	X	X	X	X	X	X	X	X	X
Point of care IL28 polymorphism test (Epistem)[e, g]		X									
Total blood draw in ml for real-time tests	-	20	10	10	20	22.5	22.5	10	10	22.5	22.5
If HIV-infected - HIV viral load (9ml)	(X)						X				X
(additional) - CD4 cell count [f]	(X)						(X)				(X)

() indicate tests that will have already been performed as part of standard management, but results will be recorded for the trial. Screening blood tests should have been performed within 60 days prior to randomisation.

On treatment visits should be within ±1 day of the nominal visit day and end of treatment (EOT) visits within ±3 days of the nominal visit day. The Day 3 visit must occur 3 or more calendar days before the Day 7 visit (that is, there should be two calendar days completely separating them). Any patient with a single HCV RNA >lower level of quantification (LLOQ) after two consecutive HCV RNA <LLOQ, or with a single value >2000 IU/ml and >1 log10 increase above the HCV RNA nadir on treatment or post EOT should be recalled for a second HCV RNA test at least one week after the initial value to confirm whether or not failure has occurred. Quality of life should also be assessed at this confirmation of failure visit.

* If a patient fails at any time point from day 14, then they move to the flow sheet for re-treatment below.
† Screening visit may be any time up to 60 days prior to randomisation, since patients with mild disease will be stable.
** Fibroscan or biopsy may be conducted within 180 days of randomisation

(a) Including record of concomitant medications, grade 3 or 4 or serious adverse events, adverse events (including reactions) of any grade leading to treatment modification including interruption/early discontinuation, resource utilisation, pill count.
(b) Quality of life will be assessed using the EuroQol (5 dimensions) (EQ-5D), the Medical Outcomes Study Short-Form 12 Item Survey[1] (SF-12, version 2) and the Cognitive Function Scale[2] (MOSCOG). Quality of life should also be performed at any additional visits to confirm HCV viral load failure.
(c) For real-time measurement of haemoglobin, white cell count, lymphocytes, neutrophils, platelets.
(d) For real-time measurement of alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, albumin and creatinine, and calculation of creatinine clearance (Cockcroft Gault).
(e) Only with specific consent for genetic testing.
(f) Screening CD4 cell count from within 1 year of randomisation can be used.
(g) EPISTEM test can be done at any time point if not possible on day 0.
(h) If a participant is hard to bleed, the blood tests should be prioritised as follows: Biochemistry>haematology (FBC>differential>INR)>HCV viral load> storage.
(i) If unable to bleed on day 28, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.

Table 2 Sample Collection Schedule – first-line treatment sample storage

	DAY POST RANDOMISATION*					EOT	WEEK POST EOT			
	0	3	7	14	28		4	8	12	24
Storage: sites processing all samples locally										
EDTA plasma for local storage (20ml blood)	X					X			X	
EDTA plasma for local storage (10ml blood)		X	X	X	X		X	X		X
EDTA whole blood for local DNA storage [a,b] (2.5ml)	X									
Whole blood in PAXgene blood RNA tube (Qiagen) [a] (2.5ml)	X									
Storage: PBMC (20ml) [c,d]	X	X	X			X	X			
Total storage sample blood draw in ml	45	30	30	10	10	40	30	10	20	10
Storage: sites sending key samples to Glasgow and able to retrieve remnant plasma from local laboratory if virological failure occurs										
EDTA whole bloodfor DX to Glasgow (20ml blood)	X								X	
EDTA whole blood for DX to Glasgow (10ml blood)		X	X	X			X			
EDTA whole blood for DNA storage for DX to Glasgow [a, b] (2.5ml)	X									
Whole blood in PAXgene blood RNA tube (Qiagen) for DX to Glasgow [a] (2.5ml)	X									
Total storage sample blood draw in ml	25	10	10	10	0	0	10	0	20	0
Remnant plasma obtainable from local service laboratory on request from study team [e]					X	X		X		X

(a) Only with specific consent for genetic testing.
(b) Can be taken at any time point if not possible on day 0.
(c) Only in a subset of sites with capacity to extract cells.
(d) If day 0 taken, up to a maximum of 4 other time points will be collected with EOT being most important.
The collection on day 0 can be taken at either screening or day 0.
(e) These samples are most likely to be required from patients who experience virological failure.

Sites processing samples locally will initially store samples on site before shipping to a central location refer to the 'STOP-HCV-1 Laboratory Manual for Local Processing & Storage' for more details.

Sites sending (unprocessed) key samples to the HCV Research UK Biobank (at the MRC University of Glasgow Centre for Virus Research) should refer to the 'STOP HCV-1 Laboratory manual for sites sending STOP HCV-1 samples to HCV Research UK Biobank' for more details.

Samples may be shipped outside of the UK to North America or Europe for additional tests after the end of the trial

Table 3 Trial Assessments and Sample Collection Schedule – Re-treatment

	START OF RE-TREATMENT (0) *	WEEKS FROM START OF RE-TREATMENT							
		2	4	8	12 (EOT)	16 EOT+4	20 EOT+8	24 EOT+12	36 EOT+24
12 weeks treatment [continuing]	DAA	[DAA]	DAA	DAA					
Clinical assessment[a]	X	X	X	X	X	X	X	X	X
Self-reported adherence		X	X	X	X				
Weight (Kg)	X		X	X	X	X		X	X
Urine pregnancy test if child-bearing potential	X		X		X			X	X
Quality of life[b]	X				X			X	
EDTA blood for haematology[c,g,h] (5ml)	(X)	X	X	X	X			X	X
Clotted blood for biochemistry[d,g,h] (5ml)	(X)	X	X	X	X			X	X
Coagulation markers[g] (2.5ml)	(X)								
Real-time HCV viral load[g,h] (10ml)	(X)	X	X	X	X	X	X	X	X
Storage: sites processing all samples locally									
EDTA plasma for storage[g,h] (10ml blood)	(X)	X	X	X	X	X	X	X	X
Total blood draw in ml if storing locally	32.5	30	32.5	30	32.5	20	20	32.5	32.5
Storage: sites sending key samples to Glasgow and able to retrieve remnant plasma from local laboratory									
EDTA plasma for DX to Glasgow[g,h] (10ml blood)	(X)							X [e]	
Total blood draw in ml if not storing locally	32.5	20	22.5	20	22.5	10	10	32.5	22.5
Remnant plasma obtainable from local service laboratory on request from study team [f]		X	X	X	X	X	X		X
If HIV-infected - HIV viral load (9ml) (additional) - CD4 cell count	X (X)				X (X)				X (X)

* If laboratory tests and plasma storage have already been performed in the prior 7 days as part of the first-line schedule above, then they do not need to be repeated at the start of re-treatment.

(a) Including record of concomitant medications, grade 3 or 4 or serious adverse events, adverse events of any grade leading to treatment modification including interruption/early discontinuation, resource utilisation, pill count;
(b) Quality of life will be assessed using the EuroQol (5 dimensions) (EQ-5D), the Medical Outcomes Study Short-Form 12 Item Survey[1] (SF-12, version 2) and the Cognitive Function Scale[2] (MOSCOG).
(c) For real-time measurement of haemoglobin, white cell count, lymphocytes, neutrophils, platelets
(d) For real-time measurement of alanine transaminase (ALT), alkaline phosphatase (ALP), bilirubin, albumin and creatinine, and calculation of creatinine clearance (Cockcroft Gault).
(e) For sites shipping unprocessed samples to the HCV Research UK Biobank, on the occasion a participant has a detectable HCV viral load at or after retreatment EOT, EOT +12 week storage sample should be taken, this sample however should not be sent to Glasgow, contact the STOP HCV-1 team for further shipment instructions.
(f) These samples are most likely to be required from patients who experience virological failure
(g) If a participant is hard to bleed, the blood tests should be prioritised as follows: Biochemistry>haematology (FBC>differential>INR)>HCV viral load>coagulation markers>storage.
(h) If unable to bleed on week 4, EOT or post-EOT week 12, the patient should be recalled, as these are critical visits for clinical care.

5. Data collection Overview

The guiding principle is that the study database should always be as accurate and up-to-date as possible. Several elements contribute to achieving this goal.

5.1 Principles of data collection

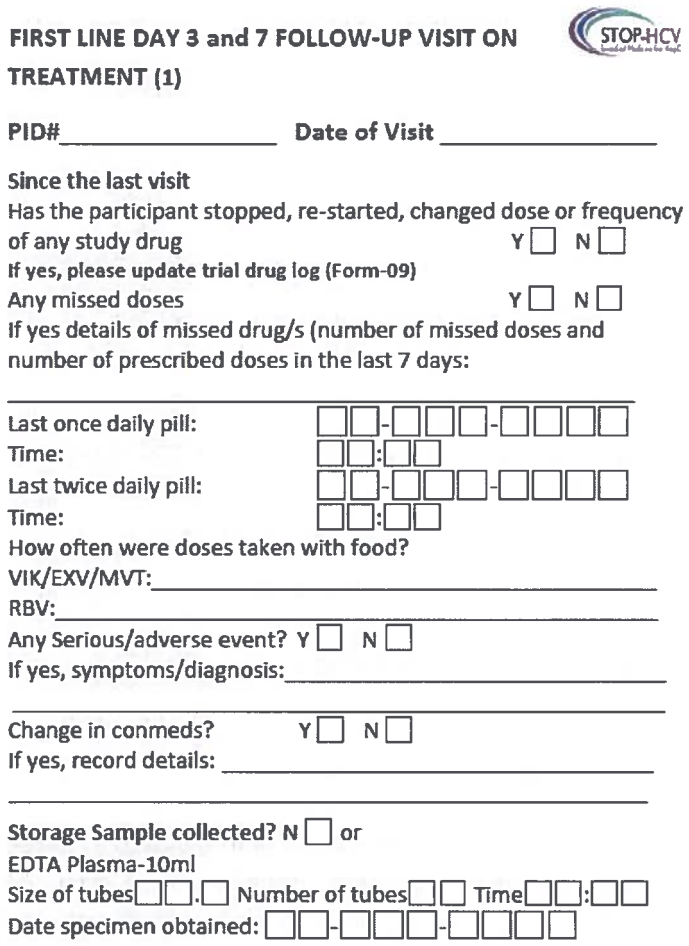
5.1.1 Source Documentation requirements

All data required on the trial Case Report Forms (CRFs) must be verifiable in the participant medical records, including:

- A statement for each eligibility criteria to document that the participant meets each inclusion criterion and does not meet each exclusion criterion
- A statement referring to the eligibility criteria; for example *"This participant meets all inclusion criteria and meets none of the exclusion criteria as defined in the protocol"*
- Randomised allocation, e.g. *"8 weeks first line treatment with weight based Ribavirin or varying first-line treatment (28-49 days; record allocated number of days) without weight-based Ribavirin."*
- Laboratory measurements- laboratory reports of HCV RNA values confirming protocol-defined failure rebounds are required to be sent to the STOP-HCV-1 study team.
- Information obtained by participant self-report.
- Any participant contact through which data are collected.
- Reference should be made if participants have completed questionnaires and date of completion.
- Serious adverse events.
- If participant or partner becomes pregnant in the duration of the trial.
- If participant is hospitalised.
- All participant record entries must be signed and dated by the clinician or research nurse who saw the participant.

To aid the collection of all trial specific information that is required to be documented in the participant's medical notes, the STOP-HCV-1 Co-ordinating Centre have created source document labels. Figure 1 below is an example of a source document label; these can be requested from the STOP-HCV-1 Co-ordinating Centre.

Figure 1 Source document label example



FIRST LINE DAY 3 and 7 FOLLOW-UP VISIT ON TREATMENT (1)

PID#_____ **Date of Visit** _____

Since the last visit
Has the participant stopped, re-started, changed dose or frequency of any study drug Y☐ N☐
If yes, please update trial drug log (Form-09)
Any missed doses Y☐ N☐
If yes details of missed drug/s (number of missed doses and number of prescribed doses in the last 7 days:

_____

Last once daily pill: ☐☐-☐☐☐-☐☐☐☐
Time: ☐☐:☐☐
Last twice daily pill: ☐☐-☐☐☐-☐☐☐☐
Time: ☐☐:☐☐
How often were doses taken with food?
VIK/EXV/MVT:_____
RBV:_____
Any Serious/adverse event? Y☐ N☐
If yes, symptoms/diagnosis:_____

_____

Change in conmeds? Y☐ N☐
If yes, record details: _____

_____

Storage Sample collected? N☐ or
EDTA Plasma-10ml
Size of tubes☐☐.☐ Number of tubes☐☐ Time☐☐:☐☐
Date specimen obtained: ☐☐-☐☐☐-☐☐☐☐

5.1.2 Source Documentation Submitted with CRFs

When submitting source documentation with CRFs (e.g. HCV RNA results) the documents/reports sent must be redacted of all participant identifiable information. A participant identification label should be attached to each page of the submitted documents/reports.

Review the document body thoroughly, as well as headers and footers for participant identifying information to ensure these are removed. Make sure that **any participant identifying information** such as participant first and last name, full birth date, hospital number, participant address and participant NHS number are completely redacted.

5.1.3 Timely and Accurate Case Report Form Completion

- CRFs should be completed by an individual well-trained in the study visit and data collection requirements. Those completing CRFs should be listed and assigned the appropriate responsibilities on the **STOP-HCV-1 Site Signature and Delegation of Responsibilities Log.**
- CRFs should be completed as soon as possible after the participant's visit or site's awareness of an event. Detailed instructions on submission timelines can be found in Tables 4 and 5.
- Each CRF must be signed and dated on the day of completion.
- It is best practice for each CRF to be reviewed by a second person familiar with the protocol prior to submission of the form.

5.1.4 Data Processing

All CRFs will be keyed by a single data entry at the STOP-HCV-1 Co-ordinating Centre ideally to the following timelines:

- Screening forms – 2 working days
- Randomisation form/Serious event form – Day of receipt
- Treatment Failure – Day of receipt
- Follow up forms and other types of form – 14 working days

5.2 Distribution of STOP-HCV-1 Case Report Forms

Sites will be provided with a folder per participant to file CRFs, with dividers to separate the various types of CRFs and visits. At the Site Initiation Visit the site will be provided with a sample folder pre-filled with CRFs, following initiation further folders will be sent to the site which will only contain dividers. The STOP-HCV-1 Co-ordinating Centre will provide blank copies of CRFs when sites request these.

The current version of the STOP-HCV-1 CRFs will be available on the STOP-HCV1 consortium website: http://www.stop-hcv.ox.ac.uk/stop-hcv-1-crfs (username: stopHCV1 password: 5TOP-!). When changes occur to CRFs the new forms will be uploaded on to the STOP-HCV-1 consortium website and each site will be sent an email documenting all the changes made to the CRFs and a date of implementation from which the old CRF versions will not be accepted. Sites should dispose all versions of the previous CRFs as soon as possible upon receipt of updated versions.

5.3 Guidelines for Completing STOP-HCV-1 Case Report Forms

Some general instructions apply to completing all STOP-HCV-1 CRFs:

1. Please ensure the most up-to-date version of the CRF is being completed. A table listing the current versions of all the CRFs will be sent to site, this should be filed in the Investigator Site File. An updated list will be sent to sites each time there are any version changes.
2. Attach a Participant Identification label to each page. These will be provided to the site by the STOP-HCV-1 Co-ordinating Centre.
3. CRFs should be completed in black or blue ink.
4. Use day-month-year (DD-MMM-YYYY) format for all dates. For example write, 02-FEB-2016. This is to avoid confusion with some trials which use US MM-DD-YYYY formats.
5. If an exact date is unavailable, use an approximate date near the time in question.
    a. If only the month and year are known, specify the 15th of that month.
    b. If only the year is known and the month is unknown but the participant can recall if it was the beginning half of the year or latter half of the year the mid-month of that half should be used. E.g. first half of the year would be March and the latter half would be September.
    c. If the time of year is unknown, use the middle of the year (01-JUL-YYYY).
    d. If the year is unknown, leave the date blank, and write in the margin that you cannot estimate a date.
    e. A note should be made next to the date to indicate that the date is estimated.
6. Use block letters and clearly print any text. Please use English for all text fields.
7. Data which is not free text will generally be collected in boxes, with one box per character. For example:

8. Where numerical data, such as the example above, is requested on a CRF, if the response is less than the maximum digits please put zeros in the leading boxes, for example, if the answer to the above question was 80 then the CRF should be completed as 080.0kg.
9. If a test result contains more digits **after the decimal** than the number of boxes provided, round up for 5 or greater, round down for less than 5. For example, 1.25 would become "1.3", 1.23 would become "1.2."
10. If a test result contains more digits **in front of the decimal** than the number of boxes provided (for example, a result over 1000, with only three boxes in which to record the result), leave the boxes blank and write the actual value next to the boxes.
11. Some lab values are reported as '<' or '>', these symbols cannot be entered onto the database.

a. If the symbol is used on the lab report or the result is listed as below the limit of quantification for HIV or HCV Viral Load results, the lowest value the assay can detect should be entered under 'Absolute result or limit of quantification' and 'Assay lower limit' marked, for example:

	Absolute result or limit of quantification (IU/mL)	Mark which is recorded
2a. Viral Load	00,000,025	b. ☐ Absolute result ☑ Assay lower limit

b. If the symbol is used to report eGFR results on lab reports this should not be reported on the CRF instead the eGFR result should be calculated using the cockroft-gault equation, the following web tool can be used to calculate this: http://nephron.com/cgi-bin/CGSI.cgi

12. When a HCV viral load is returned that is below the limit of quantification, some labs report the result as detected or not detected. If this data is reported the appropriate box should be marked on the lab form (Section C question 2e. example below). If your assay does report whether the viral load is detected below the lower limit of quantification, please mark not specified.

e. If the Viral Load is below the lower limit of quantification is it reported as:

☐ Detected, below LLOQ ☐ Not Detected ☐ Not Specified

13. Answers must be provided for all questions unless specifically directed by the instructions on the form to leave a question or section blank. If an answer to a specific question is not available, leave the values boxes blank and write the reason in the margin, for example, "participant refused," "lab specimen lost" or "test not done due to <insert explanation>". You are encouraged to write in the margins of the forms to explain missing items. Please provide an **explanation** for missing items. Merely writing "not obtained" or "not done" next to a missing item will usually generate a query requesting more information.

14. For laboratory measurements, report **the date the specimen was obtained** from the participant. **Do not** report the date the results were received.

    a. If a lab test was not performed, leave the answer boxes for that result **blank**. **Do not** write in zeros or "ND" for "not done" in the boxes. Write a brief explanation (see above) in the margin of the CRF to explain the missing lab test.

    b. If a laboratory result is pending, you may write "pending" next to the result box and submit the CRF. A margin note of "pending" will still generate a query as a reminder to report the result when it is available. Once the lab result becomes available, you will need to report the result using standard error correction procedures. See Section 5.6 of this Chapter for detailed instructions on making changes to completed forms.

Once a copy of the CRF has been submitted to the STOP-HCV-1 Co-ordinating Centre file the original in the participants CRF folder.

5.4 Completing and Submitting Case Report Forms

CRFs can be sent by encrypted email to **mrcctu.stophcv1@ucl.ac.uk** or faxed (020 7670 4817) to the STOP-HCV-1 Co-ordinating Centre or transferred using other secure methods. All CRFs must be accompanied by a completed STOP-HCV-1 Transmittal Cover Sheet (figure 2).

Figure 2 Transmittal Cover Sheet

STOP-HCV-1 TRANSMITTAL COVER SHEET

Participant ID (attach label below)	CRFs Included (mark all that apply)	#pages sent
Attach Participant ID label	☐ Screening ☐ Questionnaires ☐ Follow up visit ☐ Event Report ☐ Treatment Failure ☐ Data query ☐ Trial Drug log ☐ Other	
Attach Participant ID label	☐ Screening ☐ Questionnaires ☐ Follow up visit ☐ Event Report ☐ Treatment Failure ☐ Data query ☐ Trial Drug log ☐ Other	
Attach Participant ID label	☐ Screening ☐ Questionnaires ☐ Follow up visit ☐ Event Report ☐ Treatment Failure ☐ Data query ☐ Trial Drug log ☐ Other	
Attach Participant ID label	☐ Screening ☐ Questionnaires ☐ Follow up visit ☐ Event Report ☐ Treatment Failure ☐ Data query ☐ Trial Drug log ☐ Other	

Comments: Total Pages: ________

Date Sent : ______________ Name : ________________

5.4.1 Instructions for Completing the STOP-HCV-1 CRF Transmittal Cover Sheet

1. For each participant for whom CRFs are being sent, attach the participant's identification (PID) label in the first column.
2. In the second column, in the boxes provided mark which forms are included in this transmission for the participant.
3. In the third column, write the number of pages being sent for the participant.
4. When the number of pages sent for each participant has been completed, write the total number of pages being sent in this transmission at the bottom of the page.
5. Record the date the CRFs are being sent.
6. Record the name of the person sending the CRF pages.

For **Form 03 - Randomisation** there is a separate **Randomisation Request Form** which should be completed and submitted alongside the CRF (see section 9.1.1).

Copies of the STOP-HCV-1 CRF Transmittal Cover Sheet and the Randomisation Request Form will be sent to sites.

5.4.2 Completing the Header and Footer

Each CRF has a header that contains:

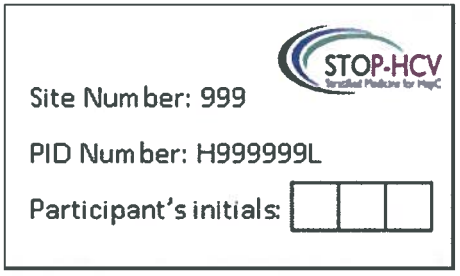
- Space for the PID label
- Visit date or Randomisation date

PID Labels

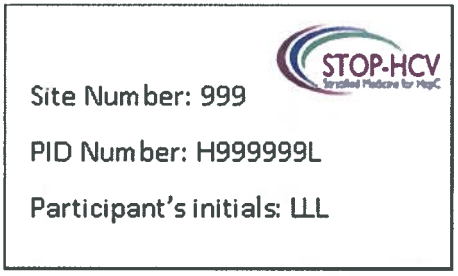
A PID label should be attached to every CRF page. Sheets of PID labels will be provided to the site by the STOP-HCV-1 Co-ordinating Centre.

All PID labels will have the Site Number and PID Number completed. Prior to the participant being randomised the site will need to hand write the participants initials in the boxes provided on the label. If the participant only has two initials please right fill the boxes provided and enter a '-' into the empty box. After the participant has been randomised, PID labels containing the participant initials will be generated and sent to sites for use on their following visits.

Screening PID label:



Post-Screening PID label:



Header

On some CRFs the visit attended (visit name) must be completed there are a number of variations for reporting which visit has taken place depending on the type of CRF being completed.

Form 01 (Screening), Form 03 (Randomisation), Form 04 (Enrolment), Form 14 (Treatment Failure) and Form 16 (Participant Status)
As these CRFs only apply to one visit type, only the date is required to be completed.

Form 02 (Laboratory Results)
To complete the visit name for this header:

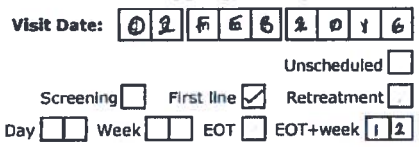
1. Mark which visit the laboratory results are associated to: Unscheduled visit, Screening visit or a part of a First line or Retreatment follow up visit.
    a) If the results are for a First line follow-up visit, First line should be marked and one of the following should be completed:
        - Day - this should be completed for all scheduled first line visits when the participant is on trial medication.

- EOT (End of Treatment) – only mark if this is the participant's first line end of treatment visit.
- EOT week – this should be completed for all scheduled visits following the first line EOT visit

b) If the results are for a Retreatment follow up visit, Retreatment should be marked and one of the following should be completed:

- Week – this should be completed for all scheduled retreatment visits when the participant is on trial medication.
- EOT – only mark if this is the participant's retreatment end of treatment visit.
- EOT week - this should be completed for all scheduled visits following the retreatment EOT visit.

For example: If the participant has completed their First line treatment and they are attending their 12 weeks post EOT visit, the header would be completed as follows:



Form 05 (EQ-5D), Form 06 (MOSCOG), Form 07 (SF-12)

The visit names for these CRFs are similar to the above, but these CRFs will only be completed at Day 0 and specific follow-up visits.

For example: If the participant was attending their End of first line treatment visit the header would be completed as follows:

Form 12 (Follow-up on treatment/EOT), Form 13 (Follow-up Post Treatment)

Form 12 will be completed at all follow-up visits whilst the participant is taking treatment. The header should be completed to represent the following possibilities:

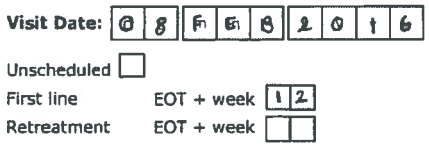
- If the participant is attending a visit which is not within a visit window on the participant's Individual Visit Schedule and they are still taking trial drug 'Unscheduled' should be marked.
- If the participant is on First line treatment enter the visit day or mark EOT for end of first line treatment.
- If the participant is on Retreatment enter the visit week or mark EOT for end of retreatment.

For example: If the participant had failed first line treatment and was 4 weeks into Retreatment the header would be completed as follows:

Form 13 will be completed at all follow-up visits after the participant has finished treatment (first line or retreatment). The header should be completed to represent the following possibilities:

- If the participant is attending a visit which is not within a visit window on the participant's Individual Visit Schedule and they are no longer taking trial drug 'Unscheduled' should be marked.
- If the participant has finished First line treatment, enter the week number post EOT.
- If the participant has finished Retreatment enter the week number post EOT.

For example: If the participant has finished First line treatment 12 weeks ago the header would be completed as follows:



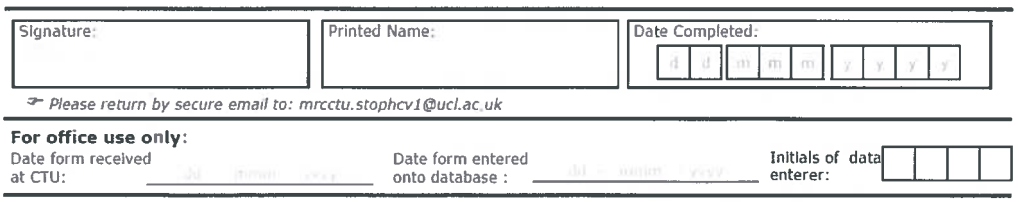
Form 10a (Serious Adverse Event) and Form 11 (Non-Serious Adverse Event)
Within the headers these CRFs only have the following two fields to be completed:

- Enter the date of onset of the Main Event (for Serious Adverse Event) or Adverse Event
- The event number on this date. If the participant has 2 events on one day, the first event would be event number 01 and second event would be event number 02.

Form 08 (Concomitant Medication Log), Form 09 (Trial Drug Log), Form 15 (Missed Visit Log)
These CRFs are used to log medications or missed visits throughout the participant's time on the trial. On the CRFs there are boxes for the page number, the first page sent should be numbered 01, and consecutive CRFs numbered 02 onwards.

Footer

The footer at the bottom of each CRF requires the signature and name of the person completing the CRF along with the date of completion. This is required for all CRFs except the questionnaires and CRFs which log information (e.g. Form 08, 09 and 15). However the logs do require initials next to each entry. The person signing the bottom of each CRF must also have signed off on the **STOP-HCV-1 Site Signature and Delegation of Responsibilities Log.**



5.5 Laboratories used for study measurements

All routine lab assessments within the study must be performed by an accredited lab. Accreditation certificates must be filed in the Investigator Site File and sent to the STOP-HCV-1 Co-ordinating Centre. Laboratory results should always be entered onto **Form 02 - Laboratory Results**. Not all tests listed on Form 02 are required at every study visit. Each section on the CRF lists the visits at which the tests in that section are required. Please also refer to the Trial Assessment Schedules (Table 1, Table 2 and Table 3). When only the HCV Viral load is required at a visit the first page can be signed and dated in the specified area and only this page submitted.

5.6 Data Queries, Resolution and Error Correction

Once the CRFs are sent to the STOP-HCV-1 Co-ordinating Centre, they will be entered on to the study database, verified and validated.
If the database validations find any errors (e.g. missing items, values out of range, data inconsistencies, logic errors for example dates in the future) a report will be generated that indicates the item that is incorrect and provides details on the nature of the error. Data queries generated for **Form 01 - Screening** and **Form 02 – Laboratory Results** for the screening visit will be sent back to sites as soon as possible after data entry so that any errors can be corrected prior to Randomisation. Data Query Reports will be sent to sites on at least a monthly basis. The site should respond to data queries within 7 days of receiving them. If the queried value is in fact correct please write a comment on the original CRF to confirm the value is correct, signing and dating the comment.

Also on a monthly basis a Missing form/Missing visit Report will be sent to sites which lists all the missing visit and missing form queries for the site. Missing visit queries are raised on Follow-up Forms (Form 12 and Form 13) only. They are automatically generated by the database allowing for submission timelines listed in table 4 and 5 below. They will be resolved once the missing visit has been submitted. Missing form queries are automatically generated by the database for forms associated to a visit. They only raise once the visit form (Form 12 or Form 13) has been entered. They are resolved once the missing form is entered on to the database.

All corrections must be made on the original CRF page. The original CRF should be retained at the site.

5.6.1 Making corrections to a CRF

If you need to change an item on a CRF due to a query or because you have additional information, you must do the following:

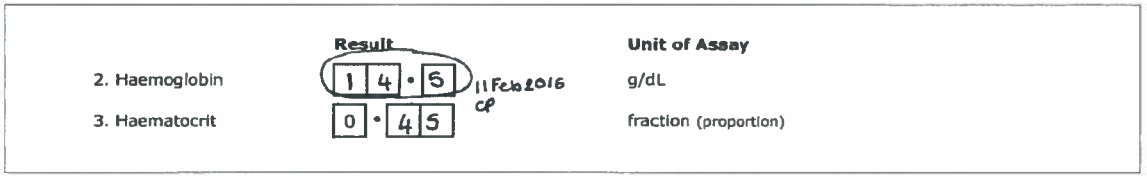
1. Draw a **single line** through the incorrect item.
2. **Clearly** write in the correct information.
3. **Circle** the ***correct*** information even if the item was previously blank. This allows data entry staff to quickly identify new or changed information.

4. Write the **date** you made the correction and **your initials** next to the correction.
5. Submit the corrected page(s) of the CRF in the same way you submitted the original, **marking "Data query"** on the STOP-HCV-1 CRF Transmittal Cover Sheet.
6. If you have submitted a CRF in error and all data should be removed from the database, you must **write "delete form"** across the entire page, write a reason for the deletion, and date and initial and resubmit the CRF page. **For multi-page CRFs, you only need to submit the first page in order to delete the entire form.**

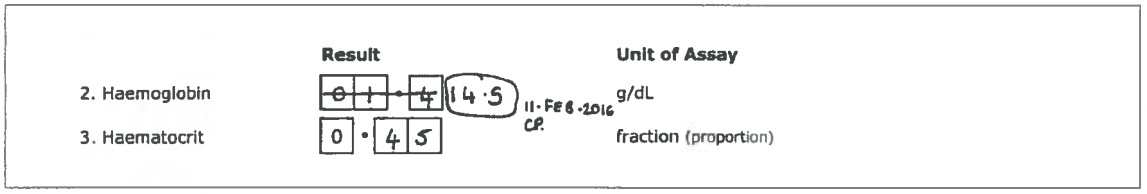
Data should **never** be erased from the CRF either by obscuring the original answer or by using correction fluid.

Examples of Error-Corrections

This is an example of an error-correction if **data was missing** at the time of CRF submission and later became available.



This is an example of an error-correction if **data changes** after the CRF has been submitted.



5.7 Overview of STOP-HCV-1 Case Report Forms

Table 4 CRFs required at each study visit and submission timelines

Visit	CRF Number	CRF Name	Submission timeline
Screening	Form 01 Form 02	Screening Laboratory Results	As soon as possible and at least 2 days prior to randomisation. Randomisation cannot proceed until the data is entered onto the database and query free.
Randomisation/ First line Day 0	Form 03 Form 04 Form 02 Form 05 Form 06 Form 07	Randomisation Enrolment Laboratory Results EQ-5D MOSCOG SF-12	Form 03 must be submitted immediately on the day of randomisation so a member of the STOP-HCV-1 team can process the randomisation. Form 04, 02, 05, 06 and 07 must be submitted as soon as possible within 14 days of the visit.
First line- Day post randomisation: Day 3, 7, 14, 28	Form 12 Form 02 Form 09	Follow-up on treatment/EOT Laboratory Results Trial Drug Log	All visits must be submitted as soon as possible within 14 days of the visit. Form 09 should be submitted on First line Day 03 to indicate the date the participant started trial drug.
First Line End of Treatment	Form 12 Form 02 Form 05 Form 06 Form 07 Form 09	Follow-up on treatment/EOT Laboratory Results EQ-5D MOSCOG SF-12 Trial Drug Log	All forms must be submitted as soon as possible within 14 days of the visit.
First Line post EOT: weeks 4, 8	Form 13 Form 02	Follow-up Post Treatment Laboratory Results	All forms must be submitted as soon as possible within 14 days of the visit.
First Line post EOT: week 12	Form 13 Form 02 Form 05	Follow-up Post Treatment Laboratory Results	All forms must be submitted as soon as possible within 14 days

	Form 06 Form 07	EQ-5D MOSCOG SF-12	of the visit.
First Line post EOT: week 24	Form 13 Form 02	Follow-up Post Treatment Laboratory Results	All forms must be submitted as soon as possible within 14 days of the visit.
If participant fails First Line treatment (Form 14 completed)			
Start of Retreatment (week 0)	Form 12 Form 02 Form 05 Form 06 Form 07	Follow-up on treatment/EOT Laboratory Results EQ-5D MOSCOG SF-12	All forms must be submitted as soon as possible within 14 days of the visit.
Retreatment: weeks 2, 4, 8	Form 12 Form 02 Form 09	Follow-up on treatment/EOT Laboratory Results Trial Drug Log – week 2	All visits must be submitted as soon as possible within 14 days of the visit. Form 09 should be submitted on Retreatment week 02 to indicate the date the participant started trial drug.
Retreatment End of Treatment week 12	Form 12 Form 02 Form 05 Form 06 Form 07 Form 09	Follow-up on treatment/EOT Laboratory Results EQ-5D MOSCOG SF-12 Trial Drug Log	All forms must be submitted as soon as possible within 14 days of the visit.
Retreatment post EOT: week 4, 8	Form 13 Form 02	Follow-up Post Treatment Laboratory Results	All forms must be submitted as soon as possible within 14 days of the visit.
Retreatment post EOT: week 12	Form 13 Form 02 Form 05 Form 06 Form 07	Follow-up Post Treatment Laboratory Results EQ-5D MOSCOG SF-12	All forms must be submitted as soon as possible within 14 days of the visit.
Retreatment post EOT: week 24	Form 13 Form 02	Follow-up Post Treatment Laboratory Results	All forms must be submitted as soon as possible within 14 days of the visit.

Other types of CRFs

Table 5 Other types of CRFs and submission timelines

CRF Number	CRF Name	Submission timeline
Form 10a	Serious Adverse Event	Within 24 hours of site awareness of event.
Form 11	Adverse Event	As soon as possible within 7 days of site awareness of event.
Form 08	Concomitant Medication Log	As soon as possible within 14 days of site awareness of change.
Form 09	Trial Drug Log	As soon as possible within 14 days of site awareness of change.
Form 14	Treatment Failure	Immediately upon second confirmatory result.
Form 15	Missed Visit Log	As soon as possible within 14 days of site awareness of missed visit.
Form 16	Participant Status	As soon as possible within 7 days of site awareness of the change in status.

6. Informed Consent

Informed consent forms must be signed and dated in ink by the participant ensuring the correct version of the Patient Information Sheet and Consent Form is used. If in doubt about the consent version; please contact the STOP-HCV-1 Co-ordinating Centre.

It is recommended that participants are given a minimum of 24 hours to review the Patient Information Sheet before signing the consent form. Optional sections of the consent form should be discussed with the participant. Please note that the EPISTEM test is only available at specific sites; if not available at your site please ensure a member of the study team marks the "Not Available" option.

Only investigators delegated the responsibility of taking consent on the STOP-HCV-1 Signature and Delegation Log are permitted to consent participants.

Three copies of the consent form should be signed by the participant and investigator, ensuring that all required boxes have been initialled and each optional consent item has been marked except at specific sites which are not performing the EPISTEM test (see above). A participant identification label should be attached to each copy of the consent form. 1 copy should be offered to the participant, 1 copy filed in the Investigator Site File, and 1 copy placed in the participant's medical records. If the medical notes are held electronically a copy of the consent form should be scanned onto the electronic system. The full Patient Information Sheet should ideally be filed in both places, not just the consent form page.

The informed consent process should be documented in the participant's medical record, and should include:

- Date of consent.
- If the participant had any questions and responses to these questions.
- If the participant opted not to take a copy of the consent document.

It must be made completely and unambiguously clear that the patient is free to refuse to participate in all or any aspect of the trial, at any time and for any reason, without incurring any penalty or affecting their treatment.

If the participant gives consent for the GP to be informed of their involvement in the trial, a letter should be sent to the GP using the REC approved letter template.

Things to remember before and during consent:

1. Check you have the right version of the Patient Information Sheet (PIS) and consent form.
2. Ensure the participant has received all pages of the PIS and there are no missing pages before they sign consent.
3. All consent discussions are documented in the medical notes.

4. Ensure the participant has initialled each required box (not signed or ticked) and answered each of the optional consent items required.
5. The signature and date of consent must be made by the participant (alterations must only be made by the participant).
6. The consenting investigator must be present at the time of consent and must sign and date the informed consent on the same day as the participant.
7. The consenting investigator must have signed the signature and delegation log and must have been delegated this responsibility by the Principal Investigator.
8. Study specific procedures must not be performed prior to the participant signing informed consent.
9. Ensure the informed consent process has been sufficiently documented in the participant's medical records.

7. Eligibility Criteria

There will be **no exceptions to eligibility** requirements at the time of randomisation. This is for the safety of the patients, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar disease status in future.

Patients will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria defined below.

It is essential to document in the source notes that the participant meets every inclusion and none of the exclusion criteria, preferably with an individual comment for each criterion. All entries in the medical records must be signed and dated by the person making the entry. Hard copy laboratory reports should be filed in the medical records. Source documentation requirements are outlined below under each criterion. The Consent and Screening source document label may be used for any of the criteria below, except those that require hard copy laboratory results.

7.1 Patient Inclusion Criteria

1. Aged ≥18 years.

   The participant's date of birth must be verifiable in their medical records.

2. Infected with HCV genotype 1a or 1b or 4 with access to first-line treatment appropriate for their genotype (ombitasvir/paritaprevir/(dasabuvir)/ritonavir or glecaprevir/pibrentasvir)

   Laboratory results documenting that the participant has been infected with HCV RNA genotype 1a or 1b or 4 should be filed in the participant's medical records.

3. At least one detectable viremia 6 months prior to randomisation (by quantitative HCV RNA, qualitative assay or HCV genotype), with no intervening undetectable results.

   Laboratory results documenting that the participant has been infected with HCV for at least 6 months should be filed in the participant's medical records.

4. Plasma HCV RNA >LLOQ at screening.

   HCV viral load test should be conducted within 60 days of randomisation, and the laboratory reports must be filed in participant's medical records.

5. No evidence of significant liver fibrosis resulting from any aetiology (defined as Fibroscan score ≤7.1kPa, equivalent to F0-F1[33], within 180 days prior to planned randomisation or biopsy consistent with mild fibrosis (Ishak score <=2/6) within 180 days prior to planned randomisation).

   A fibroscan test or biopsy conducted as part of the participant's routine care can be used but must be within 180 days prior to the randomisation date. The Fibroscan must be a valid result (based on at least 10 readings) performed by an

experienced technician. It is expected that fibroscan technicians will have completed all necessary training within the NHS Trust before performing scans.

6. BMI >=18kg/m^2.

Participant's BMI should be recorded in the medical records.

7. Laboratory tests: platelets >=60x10^9/l, haemoglobin >12g/dl (male) or >11g/dl (female), creatinine clearance (estimated using Cockcroft-Gault) >=60ml/min, international normalised ratio (INR) <1.5.

The web tool http://nephron.com/cgi-bin/CGSI.cgi ***should be used to calculate Cockcroft-Gault. Please note, when using the webtool µmol/L should be selected for plasma creatinine (PCR). Results must be recorded in the participant's medical records and the method of calculation stated. The specimen for these laboratory tests should be taken within 60 days prior to randomisation.***

Laboratory reports must be filed in the participant's medical records.

8. Screening HCV viral load <10,000,000IU/ml.

Laboratory result must be filed in the participant's medical records.

9. Written informed consent obtained from the patient.

Informed consents must be signed and dated in ink by the participant before any study specific procedures are performed. Ensure you have the correct version of consent. A copy must be kept in the participant's medical records, Investigator Site File and a copy given to the participant.

If participant is HIV infected, then an additional eligibility criterion is:

10. On antiretroviral therapy with HIV viral load <50 copies/ml for >24 weeks at the screening visit.

Laboratory confirmation of HIV RNA <50 copies/ml must be available in participant's medical records. It is permitted for a participant to have changed antiretroviral regimens in the last 24 weeks, provided that they have never had an HIV viral load >=50 copies/ml.

7.2 Patient Exclusion Criteria

1. Previous DAA exposure for this infection (previous treatment with pegylated-interferon and/or ribavirin allowed. DAA treatment for a previously cured infection allowed).

If participant has had DAA exposure for a previous infection, documentation must be available in the medical records confirming that the participant was cured and that the current infection is new.

2. FEMALES ONLY: Lactating, or pregnant, or planning to become pregnant, or not willing to use effective contraception during the study and for four months after last dose of study medication.

   See Section 7.3 for guidance on what is considered effective contraception in the trial. A pregnancy test must be done on day 0 for all women of a child bearing potential and the results documented in the medical records. If the participant is of child bearing potential the method of effective contraception must be documented in the participant's medical records.

3. FEMALES ONLY: Currently taking ethinyl-oestradiol-containing medicinal products such as those contained in most combined oral contraceptives or contraceptive vaginal rings.

   Document that the participant is not taking any ethinyl-oestradiol-containing medicinal products.

4. MALES only: planning pregnancy with female partner, or not willing to use effective contraception during the study and for seven months after last dose of study medication.

   Document that the participant is not planning a pregnancy with a female partner during the study of for 7 months after the end of the study and document the method of contraception during the study and for 7 months after the last dose of the study medication. See Section 7.3 for guidance on what is considered effective contraception in the trial.

5. Malignancy within 5 years prior to screening.

   Note in the medical records that the participant has had no malignancy within the last 5 years.

6. Any condition in the judgement of the investigator which might limit the patient's life expectancy.

   Note in the medical records that the participant has no condition that may limit their life expectancy.

7. Currently receiving medication known to interact with study medication (ombitasvir, paritaprevir, dasabuvir, ritonavir, sofosbuvir, ledipasvir, ribavirin, glecaprevir, pibrentasvir).

   Review relevant prescribing information (Summary of Product Characteristics) and Sections 5.3.4, 5.4.4 and 5.5.4 of the study protocol. The website www.hep-druginteractions.org is also useful for ascertaining if there are any possible drug interactions with a participant's current medication. Record all concomitant medications that the participant is taking in the medical records. Document if any of the participants concomitant medications interacts with the study medication.

8. Disorder which may cause ongoing liver disease including, but not limited to, active hepatitis B or ongoing alcohol misuse.

   Note in the medical records that the participant does not have a disorder that may cause ongoing liver disease. Alcohol misuse should be down to the judgement of

the investigator, noting the effect on the participant committing to attending trial visits and their ability to adhere to the trial regimen (see criteria 9 below).

9. Any disorder which in the opinion of the investigator may have a significant negative impact on the ability of the patient to adhere to the trial regimen.

   Note in the medical records that there is no reason in the opinion of the investigator that the participant will not adhere correctly to the trial regimen.

10. Use of other investigational products within 60 days of screening.

    Note in the medical records that the participant has not used any other investigational products within 60 days.

11. Known hypersensitivity to any active ingredient and/or excipients of the study medicines, namely Microcrystalline cellulose, Lactose monohydrate, Croscarmellose sodium, Magnesium stearate, Gelatine, Shellac, Propylene glycol, Polyethylene glycol, Ammonium hydroxide, Pregelatinised maize starch, Sodium starch glycolate (type A), Maize starch, Hypromellose, Talc, Ethylcellulose aqueous dispersion, Triacetin, Copovidone, Colloidal anhydrous silica, vitamin E (tocopherol) polyethlyene glycol succinate, sodium stearyl fumarate, Polyvinyl alcohol, Macrogol 3350, Sunset yellow FCF aluminium lake (E110), Colouring agent (E132), Titanium dioxide (E171), Yellow iron oxide (E172), Red iron oxide (E172), Black iron oxide (E172).

    Note in the medical records that the participant does not have a known hypersensitivity to any ingredient of the study medicines.

12. History of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease, in the previous six months.

    Note in the medical records that the participant does not have a history of severe pre-existing cardiac disease in the previous 6 months.

13. Haemoglobinopathies (e.g., thalassemia, sickle-cell anaemia).

    Note in the medical records that the participant has no haemoglobinopathies.

If there are any questions/queries about a participant's eligibility please address this to the STOP-HCV-1 Co-ordinating team who will direct relevant queries to the Chief Investigator or the STOP-HCV-1Trial Physician.

7.3 Important Note: Contraception

All trial participants must be willing to use effective contraception during the trial and for at least four (women) or seven (men) months after the last dose of trial medication if they are either a woman of childbearing potential (WOCBP) or the fertile partner of a WOCBP.
The oral DAAs are pregnancy category B drugs. Ribavirin is a Category X drug in pregnancy. As all patients will be randomised to receive or not receive adjunctive Ribavirin, being pregnant or intending to become pregnant (self or partner) is an exclusion criteria. Hence, WOCBP must avoid pregnancy for the duration of the study and for ≥4 months after Ribavirin exposure.

- A WOCBP is defined as a woman who is fertile, following menarche and until becoming post-menopausal unless permanently sterile.
- Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient.
- A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Effective contraceptive methods are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly.

Examples of such methods include:

- Combined (oestrogen and progestogen containing) hormonal oral, intravaginal or transdermal contraception associated with inhibition of ovulation **unless** this contains ethinyl-oestradiol which is an exclusion criteria, see above.
- Progestogen-only hormonal oral, injectable or implantable contraception associated with inhibition of ovulation **unless** this contains ethinyl-oestradiol which is an exclusion criteria, see above.
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomised partner – this is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
- Sexual abstinence where this involves refraining from heterosexual intercourse during the entire period of risk. For sexual abstinence to be acceptable as an

effective contraception, abstinence must be specified as the preferred and usual lifestyle of the patient.

Note: Condom use alone is not an effective method of contraception.

7.4 HIV co-infected patients

Sites should aim to recruit no more than one half of their patients with HIV coinfection.

The SmPCs for the trial drugs should be checked to confirm which HIV ARVs can be safely administered. Please also refer to the STOP-HCV-1 trial protocol for a summary of which ART can be administered in HIV-HCV co-infected patients during the trial.

Participants should not be changed mid trial from one ART combination to another.

Additional Note: A recent directive has been issued to change HIV positive patients to cheaper regimens. Changing participant's regimens should be delayed until after receiving HCV treatment.

- For patients on a PI/r based regimen, many clinics are now being advised to switch patients on ritonavir boosted DRV or ATV to the now cheaper cobicistat boosted fixed dose combination, Rezolsta (DRV/r) or Evotaz (ATV/r). To avoid switching STOP-HCV-1 co-infected patients on a PI/r based regimen 3 times e.g. DRV/r to Rezolsta to DRV alone (while on A3D) back to Rezolsta we recommend that such patients do not initiate the switch to Rezolsta or Evotaz until after first-line treatment is completed. A second, and important reason is that use of a DRV/c or ATV/c FDC, might lead to inadvertent co-administration of a double boosting agent, cobicistat in the FDC and ritonavir in the A3D FDC;
- This directive should not apply to those on raltegravir or dolutegravir based regimens, as there are no cheaper versions of these generic drugs yet.

8. Screening

If any tests and procedures are conducted specifically for the trial alone (and not as part of routine care) you **must** ensure that written informed consent has been taken from the participant prior to the test or procedure being conducted. It is a consent/screening violation if study specific procedures are completed prior to consent.

As patients with mild chronic HCV disease are relatively stable, some assessments done as part of routine clinical management and completed prior to the participant consenting for STOP-HCV-1 can be used as part of the participant's screening assessment and recorded for the trial with the prerequisite that they are within the specified screening window of within 60 days of randomisation. Exceptions to the 60 days are the liver fibrosis assessment which can be done within 180 days and, if HIV infected, the CD4 count which can be within 1 year.

To ensure tests are within the required window a web tool date calculator, is recommended to check if a test/assessment is within the screening window, an example web tool can be found at the following website: http://www.timeanddate.com/date/dateadd.html. The calculator allows you to add or subtract days, months and years to a date to calculate a past or future date.

The screening visit can be conducted at any time (within the time restrictions above for test results) up to the day before randomisation, providing that results of blood tests to confirm eligibility in terms of laboratory abnormalities and HCV VL are available.

8.1 Blueteq registration

- Sites should ensure participants are registered on Blueteq at screening, using a first-line treatment form before any medication is dispensed. This will notify NHSE that the participant is eligible against the study inclusion and exclusion criteria and will register the participant on the trial.
- **Note:** The participant's NHS number, hospital number, GP code and postcode will be required for the Blueteq form.

Guidance on Blueteq form completion:

Question 3: it is suggested that option 1 – "Fixed duration of 8 weeks" is initially selected.

Question 4: it is suggested that option 1 "Treatment with ribavirin" is initially selected.

- Once the participant has been randomised, the form will then need to be updated with the participant's actual randomisation allocation.
- If a participant fails treatment, they will need to be registered again on Blueteq using the Re-treatment form before re-treatment is commenced.

8.2 Screening & Randomisation Log

A participant is considered to have entered the screening process once they have signed the STOP-HCV-1 informed consent form. Every participant who is screened for STOP-HCV-1 must therefore be entered onto the **STOP-HCV-1 Screening and Randomisation Log** (see figure 3).

The STOP-HCV-1 Co-ordinating Centre will provide each site with logs prefilled with participant identification numbers. When a participant signs consent, they should be assigned an identification number and added to the Screening and Randomisation Log completing the following information:

- NHS Number
- Initials
- Date of Birth
- Consent date
- If the participant will be randomised

Following randomisation the log should be updated to add:

- Randomisation date
- Treatment prescribed
- Randomised allocation

Figure 3 Screening and Randomisation Log

STOP-HCV
Stratified Medicine for HepC

MRC Clinical Trials Unit

UCL

Screening and Randomisation Log

Site Name: ____________________

For each participant that signs Informed Consent for the STOP-HCV-1 trial, complete the row of their assigned Participant ID (PID) number.

Participant ID	NHS Number	Initials	Date of Birth	Date Consent Signed	Will the participant be randomised?	Treatment Prescribed	Randomisation Allocation
					☐ Yes ☐ No ↓ Randomisation Date:	☐ Viekirax and Exviera (genotype 1a/1b) ☐ Viekirax (genotype 4) ☐ Maviret (genotype 1a/1b/4)	Tick one ☐ Fixed (56 days) ☐ Varying for ☐☐ days Tick one ☐ With Ribavirin ☐ Without Ribavirin
					☐ Yes ☐ No ↓ Randomisation Date:	☐ Viekirax and Exviera (genotype 1a/1b) ☐ Viekirax (genotype 4) ☐ Maviret (genotype 1a/1b/4)	Tick one ☐ Fixed (56 days) ☐ Varying for ☐☐ days Tick one ☐ With Ribavirin ☐ Without Ribavirin
					☐ Yes ☐ No ↓ Randomisation Date:	☐ Viekirax and Exviera (genotype 1a/1b) ☐ Viekirax (genotype 4) ☐ Maviret (genotype 1a/1b/4)	Tick one ☐ Fixed (56 days) ☐ Varying for ☐☐ days Tick one ☐ With Ribavirin ☐ Without Ribavirin
					☐ Yes ☐ No ↓ Randomisation Date:	☐ Viekirax and Exviera (genotype 1a/1b) ☐ Viekirax (genotype 4) ☐ Maviret (genotype 1a/1b/4)	Tick one ☐ Fixed (56 days) ☐ Varying for ☐☐ days Tick one ☐ With Ribavirin ☐ Without Ribavirin

Screening and Randomisation Log v2.0 18-Oct-2017 Page Number____

8.3 Screening Assessments

The Screening visit is used to assess the participant's eligibility. It should be completed **within 60 days** of Randomisation.

8.3.1 During the Clinic visit

The following information and assessments should be collected:

- Demographics including date of birth, sex at birth and the participant's ethnicity
- Participant's weight, height and calculated BMI (taken within 60 days of randomisation)
- Hepatitis C history:
  - mode/s of transmission
- Liver fibrosis assessment – unless a fibroscan or liver biopsy has been completed within 180 days prior to planned randomisation which can be used.
- Take blood for lab assessments unless results available from routine care (within 60 days of randomisation):
  - HCV VL, Haematology, Biochemistry and Coagulation Markers
  - If HIV infected: HIV VL and Immunology (the CD4 count can be within 1 year or randomisation)
- Discuss a planned date of randomisation, taking into account the dates of all screening assessments and the participant's availability to attend all required study visits.

If the participant is HIV co-infected the following information and assessments should be completed:

- HIV date of diagnosis
- The Summary of Product Characteristics should be reviewed to ensure trial IMP can be safely administered along with the participant's anti-retroviral regimen. Review Table 10 in the STOP-HCV-1 protocol for a list of ART which can be administered. If the patient is on ART that should not be administered with study IMP, then it is permitted to change the ART and re-screen the patient at a later date. To remain eligible they must not have had an HIV viral load >=50 copies/ml for the last 24 weeks.

8.3.2 Reporting the visit

Form 01 - Screening should be completed for every participant who signs consent. The laboratory results from the bloods taken at the screening visit should be reported on the **Form 02 - Laboratory Results.** Please see below instructions for completing **Form 01 – Screening;** some sections contain additional information which would not have been collected during the clinic visit.

Section A: Demographics – report the information collected at the clinic visit.

Section B: Clinical Information – report the participant's weight, height and calculated BMI collected at the clinic visit.

Section C: Hepatitis History

C. HEPATITIS HISTORY

Hepatitis C History

1. What is/are the likely mode(s) of HCV infection?
(Please indicate all risk factors and answer all questions either Yes or No)

a. No known risk factor	☐ Yes	☐ No
b. Injecting drug use	☐ Yes	☐ No
c. Blood/blood products	☐ Yes	☐ No
d. Perinatal exposure	☐ Yes	☐ No
e. Known Hep C positive sexual partner	☐ Yes	☐ No
f. Born abroad	☐ Yes	☐ No
g. High risk sexual partner	☐ Yes	☐ No
h. Tattoo	☐ Yes	☐ No
i. Healthcare exposure	☐ Yes	☐ No
j. Other:	☐ Yes	☐ No

k. If other please specify: _____

2. Date of first HCV positive test: d d m m m y y y y

Hepatitis C History

1. Report the likely mode/s of HCV transmission. Mark all modes either 'Yes' or 'No'. If 'Other' is marked please specify.

2. Report the date of HCV positive test. This date must be at least six months prior to randomisation and be reported using a quantitative HCV RNA assay, qualitative assay or HCV genotype.

C. HEPATITIS HISTORY continued

Two most recent HCV viral load results taken prior to screening:

	Date specimen obtained	Absolute result (IU/mL)	Type of assay used
3a.	d d m m m y y y y	b. , ,	c. ☐ Cobas Amplicor v2 (Roche) ☐ Realtime HCV (Abbott) ☐ Aptima QuantDX (Hologic) ☐ Versant HCV assay v2 (siemens) ☐ Other d. Please specify _____
4a.	d d m m m y y y y	b. , ,	c. ☐ Cobas Amplicor v2 (Roche) ☐ Realtime HCV (Abbott) ☐ Aptima QuantDX (Hologic) ☐ Versant HCV assay v2 (siemens) ☐ Other d. Please specify _____

	Date specimen obtained	Genotype/ subgenotype
5. HCV genotype/subgenotype result:	a. d d m m m y y y y	b. ☐ 1a ☐ 1b ☐ 4

Hepatitis B History

6. Is the participant Hep B eAg positive? ☐ Yes ☐ No

7. Is the participant Hep B sAg positive? ☐ Yes ☐ No **If C.6 and C.7 are no, go to section D**

8. If yes to C.6 or C.7, is the participant's latest HBV viral load undetectable ☐ Yes ☐ No

9. Date of last undetectable HBV viral load: d d m m m y y y y

3/4. Report the **two** most recent HCV viral load results taken prior to screening. If only one result is available please make a note to indicate this. The HCV VL result taken at the screening clinic visit should not be entered in this section.

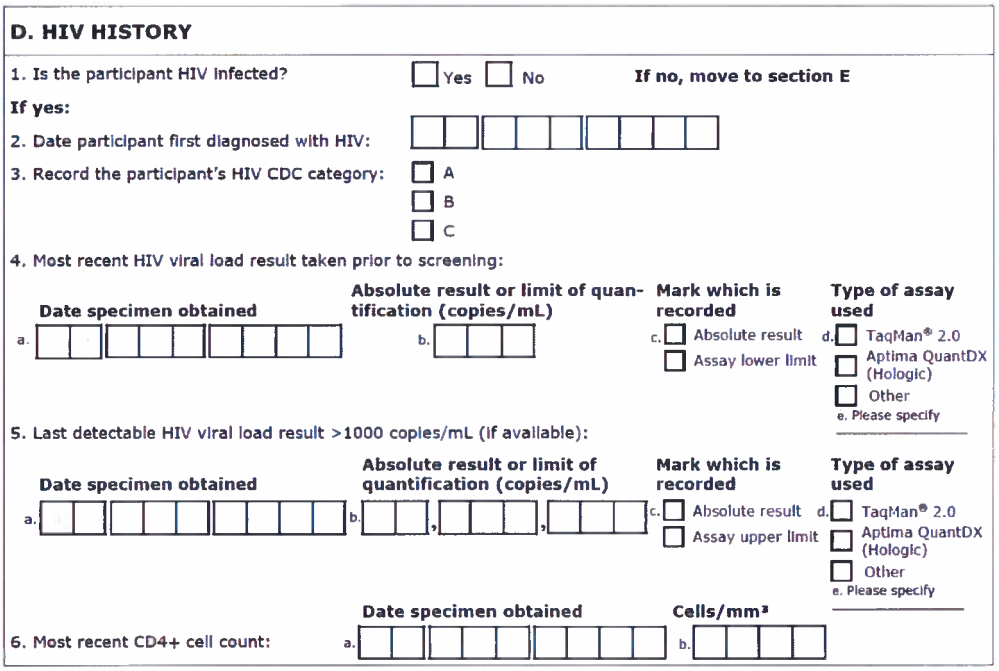
5. Report the participant's HCV genotype and the date the specimen was obtained for the result. At the point of randomisation, this will be checked against the prescribed regimen reported on the **Form 03 - Randomisation**.

Hepatitis B history

6/7. Indicate whether the participant is Hep B eAg or sAg positive. Mark 'Yes' or 'No' to both questions.

8/9. Only answer if C.6 or C.7 is 'Yes'. Mark if the participant's latest viral load is undetectable and the date of this result.

Section D: HIV History



If the participant is not HIV infected, only question 1 in this section needs to be completed. If the participant is HIV co-infected continue with this section.

2. Report the date participant was first diagnosed with HIV.

3. Report the participants HIV CDC category.

4. Report the most recent HIV VL result prior to screening. All HIV VL taken within 24 weeks of screening must be below 50 copies/ml to meet the inclusion criteria.

5. Record the date of the last detectable HIV VL above 1000 copies/ml. If there is a result to report here that is within 24 weeks of screening, the participant **does not** meet the inclusion criteria. If there is no result available please make a note to indicate this.

6. Record the most recent CD4+ cell count. The CD4+ result taken at the screening clinic visit should not be entered in this section.

Section E: Liver Fibrosis

E. LIVER FIBROSIS		
1. Has the participant ever had a fibroscan?	☐ Yes ☐ No	If no, go to question E.3
	Date scan obtained	Result
2. If yes, what was the result of their last fibroscan:	a. ☐☐ ☐☐☐ ☐☐☐☐	b. ☐☐ • ☐ kPa
3. Has the participant had a liver biopsy?	☐ Yes ☐ No	If no, go to section F
	Date biopsy obtained	Score
4. If yes, what was the Ishak score?	a. ☐☐ ☐☐☐ ☐☐☐☐	b. ☐ /6

1-4. An assessment of the participant's fibrosis stage is required within 180 days of randomisation. This can be assessed by either fibroscan or liver biopsy. Within this section, the fibroscan or liver biopsy used to determine if the participant is eligible must be entered. To meet the eligibility criteria, if the participant has a fibroscan, the result must be ≤7.1kPa (unless the patient also has a liver biopsy Ishak score <=2/6). If the participant has had a liver biopsy the Ishak score which must be < or =2/6 (unless the patient also has a fibroscan result ≤7.1kPa).

Section F: Routine Bloods – Is a reminder to complete **Form 02 – Laboratory Results** for the required blood assessments.

Section G: Randomisation – Enter the planned randomisation date which was discussed with the participant at the screening clinic visit. This is also the date which is initially used to calculate if the results are within the required windows.

8.3.3 Re-screening

If a participant has signed consent and entered the screening process, but is then found to be ineligible, the participant is able to be re-screened. Participants that are re-screened keep the same trial number. Tests may be re-done and if the repeat test is within the required specificities, this may be used and the participant will be deemed eligible for the trial. It is important to remember that all tests must still be within 60 days of randomisation (or 180 days if a fibroscan) and therefore other tests may also need to be repeated, not just the result that made the patient ineligible. The participant will not need to re-sign consent.

For example, the participant signs consent on 30-Nov-2016, has a fibroscan result from 16-Jun-2016, has blood tests done on 05-Dec-2016, and a planned randomisation date of 10-Dec-2016. From the blood tests taken on 05-Dec-2016, the eGFR is calculated to be 58 which makes the participant ineligible. The investigator believes that there were reasons for this result being out of the range and it is likely that if the creatinine is re-tested the eGFR would be above 60, therefore making the patient eligible. The patient is not able to return to clinic until the 15-Dec-2016, when the creatinine is retested and the eGFR calculated as 62. A new randomisation date of 20-Dec-2016 is planned. All the blood tests taken on 05-Dec-2016 are still within 60 days of randomisation and therefore can be used. The fibroscan however, is now over 180 days ago so cannot be used and needs to be re-done in order for the patient to be deemed eligible.

8.3.4 Screening Failures

If a participant is determined to be ineligible during screening and therefore will not be randomised, the Screening and Randomisation Log (Figure 2) should be updated to tick "no" under the column "will the participant be randomised".

Form 01 - Screening, **Form 02 - Laboratory Results** and **Form 03 - Randomisation** should be completed and submitted to the STOP-HCV-1 trial team. The reason why the participant is ineligible should be recorded in the participant's medical records.

Note: The date of the screening visit should be used for the 'Visit Date' on **Form 03 - Randomisation.**

This completes the requirements for ineligible participants.

8.3.5 Eligible participant, but not randomised

If a participant is determined to be eligible during screening but will not be randomised e.g. the participant changes their mind about participating in the study, the Screening and Randomisation Log should be completed and **Form 01 – Screening**, **Form 02 - Laboratory Results** and **Form 03 - Randomisation** should also be submitted.

It should be recorded in the participant's medical records the reason why they will not be randomised.

This completes the requirements for eligible participants not being randomised.

8.3.6 Eligible participants who will be randomised

If the participant meets the eligibility criteria and will be randomised, complete **Form 01 - Screening** and **Form 02 - Laboratory Results** and submit to the STOP-HCV-1 Co-ordinating Centre. Ideally this should be completed and submitted 2 days prior to the planned randomisation date to ensure that eligibility can be checked, data entry can be completed and any queries resolved, in preparation for randomisation. Providing a planned randomisation date at the end of **Form 01 – Screening** will mean the STOP-HCV-1 Co-ordinating Centre know to expect the randomisation, allow the team to plan suitable staff cover and ensure the randomisation is processed as quickly as possible.

A screening visit can be done up to the day before randomisation, providing blood test results confirming eligibility in terms of laboratory abnormalities and HCV VL are available for randomisation. If you anticipate randomising a patient the day after screening (e.g. because the participant has received the consent documents by email and has laboratory test results available from routine care), please inform the STOP-HCV-1 Co-ordinating Centre in advance. You must also still ensure that the **Form 01 – Screening** and **Form 02 - Laboratory Results** are submitted to the STOP-HCV-1 Co-ordinating Centre with sufficient time to allow the randomisation to be processed.

9. Randomisations

RANDOMISATIONS

To randomise, please securely email a completed Form 03 to mrcctu.stophcv1@ucl.ac.uk or fax to **0207-670-4817.** Please ensure you use the randomisation cover sheet providing a telephone number which the team can call you back on to process the randomisation.

RANDOMISATIONS SHOULD ONLY OCCUR ON DAYS WHEN SUBSEQUENT DAY 3 VISITS CAN BE SCHEDULED IN CLINIC

Randomisation times 09:00 – 17:00

Randomisation will be processed via a computer-generated programme at the STOP-HCV-1 Co-ordinating Centre and may occur on any week day; however it is important that you consider the day of the week in which a participant is randomised in relation to your site clinic days.

Day 3 and 7 are important in terms of the kinetics of the HCV RNA response (and could improve treatment stratification in the future). HCV viral load and EDTA plasma samples for storage are collected on these days in all patients; the ±1 day visit window for early on-treatment visits places restrictions on which days of the week the Day 3 visit can occur. A schema for randomisation and Day 3 and 7 visits is provided in Table 6.

Sites must only randomise patients on days of the week when it is possible for the patient to attend a Day 3 visit within the visit window. Day 3 should also occur 3 or more calendar days before the Day 7 visit, therefore two complete calendar days separating them.

Table 6 Schema for randomisation day and effects on Day 3 and 7 visits

Randomisation – Day 0 R Target visit days Visit window ± 1 day

Randomise	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa
Monday	R			D3				D7							D 14					
Tuesday		R			D3				D7							D 14				
Wednesday			R			D3				D7							D 14			
Thursday				R			D3				D7							D 14		
Friday					R			D3				D7							D 14	

Randomisation Examples:

Randomise	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa
Monday	R			D3				D7							D 14					

A participant randomised on a Monday should attend their Day 3 visit on a Thursday, however the day 3 visit has a window of ± 1 day, therefore the visit can be conducted on a Wednesday or Friday, dependant on clinic and participant convenience.

Randomise	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa
Wednesday			R			D3				D7							D 14			

If a participant is randomised on a Wednesday, their target Day 3 visit falls on a Saturday; however this visit can be conducted on a Friday. Please note participants must not be randomised on a Wednesday if they are unable to come in for a day 3 visit on a Friday.

Randomise	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa	Su	M	T	W	Th	F	Sa
Thursday				R			D3				D7							D 14		

If a participant is randomised on a Thursday the Day 3 visit will fall on a Sunday however with the visit window being +/- 1 day this visit can be conducted on Monday. If there are no clinics on a Monday or a participant is unable to attend a visit on Monday you should not randomise the participant on a Thursday.

If a participant is randomised on a Friday, they should be provided with the contact details for whom to contact in the event they have any issues with their medication over the weekend. If there is no facility for weekend contact you should avoid randomising participants on a Friday.

9.1 Randomisation Procedures

9.1.1 Randomisation CRF - Form 03

Form 03 - Randomisation confirms the participant meets all inclusion criteria (section A) and meets none of the exclusion criteria (section B).

- Review the participant's consent forms to ensure that all mandatory boxes have been initialled and they have provided a response to each of the optional criteria (section C). If consent was provided at the screening visit, please confirm with the participant that they would still like to join the trial.
- Enter the date, result and assay type of the participant's screening HCV viral load.

  Note: this should be <10, 000,000 IU/mL.
- If participant is not HIV infected, select "not applicable" for question A9.

- Following review of the eligibility criteria confirm the eligibility outcome (in section D). If the participant does not meet the eligibility criteria and will not be randomised sign and date the randomisation CRF and submit to the STOP-HCV-1 Co-ordinating Centre.
- The participant should be asked about the date and the time they intend to take their first dose; this **must not be more than 1 day** after randomisation. Record the date and approximate time in the participant's medical records and on **Form 03 - Randomisation**.
- Select the first-line treatment that the participant will be prescribed.

2. What first-line treatment will the participant be prescribed?

- ☐ Viekirax (ombitasvir/paritaprevir/ritonavir) and Exviera (dasabuvir) with or without weight-based Ribavirin (genotype 1a/1b only)
- ☐ Viekirax (ombitasvir/paritaprevir/ritonavir) with or without weight-based Ribavirin (genotype 4 only)
- ☐ Maviret (glecaprevir/pibrentasvir) with or without weight-based Ribavirin (genotype 1a/1b and 4)

A note on treatment options: Maviret has been added to protocol v6.0 in anticipation of approaching changes within NHS England, where we are expecting Maviret to be made available in the near future and possibly become the recommended first-line treatment option. **Sites should not prescribe Maviret in STOP-HCV-1 until they receive notification from the STOP-HCV-1 Co-ordinating Centre that it is now available and may now be used within the trial.** If you would like to use Maviret before you receive notification, please do get in contact to discuss this.

Once Maviret is available and notification from the STOP-HCV-1 Co-ordinating Centre has been received; there will be 3 possible first-line drug combinations that patients can be treated with in the trial. These will depend on the patient's genotype and local availability:

- Viekirax (ombitasvir/paritaprevir/ritonavir) and Exviera (dasabuvir) for genotype 1a/1b
- Viekirax (ombitasvir/paritaprevir/ritonavir) for genotype 4
- Maviret (glecaprevir/pibrentasvir) for genotype 1a/1b and 4.

With all 3 possible first-line treatments, all patients will also be randomised with or without ribavirin.

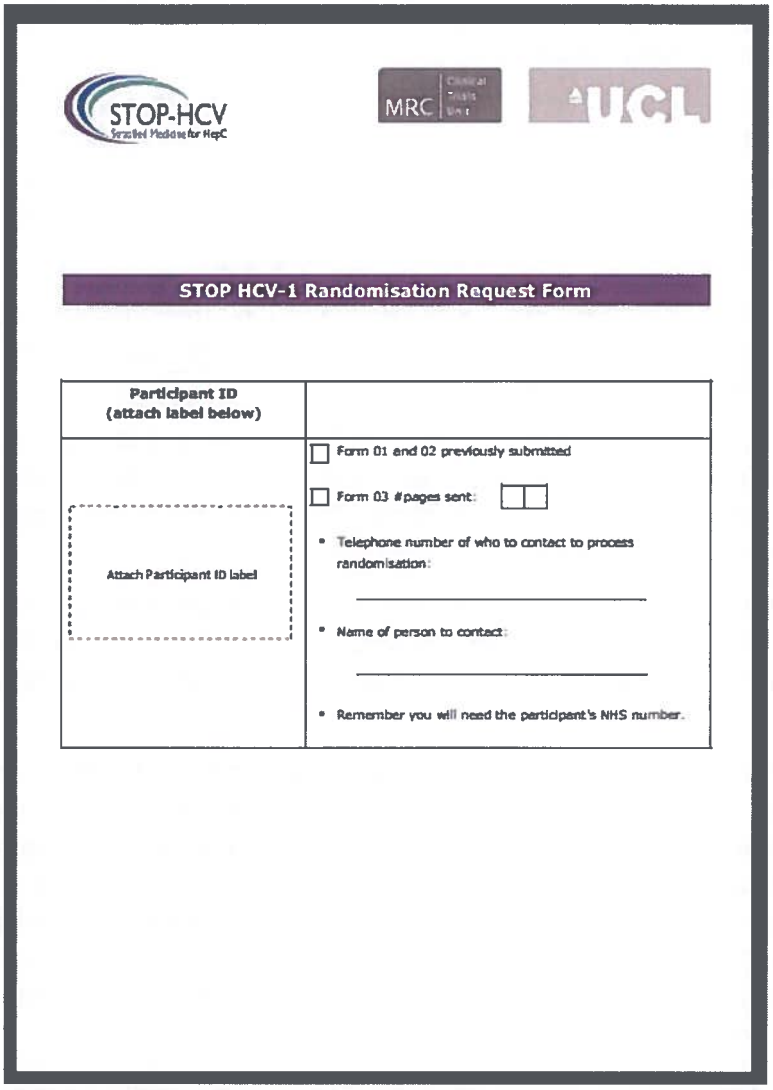
Sites should choose which first-line regimen to treat a patient with depending on genotype and local availability. **Sites should treat with the drug that is their local recommended first-line treatment option for the patient's genotype.**

The following must be ensured:

- If the participant is a woman of child-bearing potential, a negative urine pregnancy test should have been completed on the day of randomisation.
- All the quality of life questionnaires should have been completed by the patient before randomisation.
- The participants concomitant medication has not changed since the screening visit and confirm they are not taking any medication known to interact with the study medication.

9.1.2 Randomisation Request Form

Figure 4 Randomisation Request Form



STOP HCV-1 Randomisation Request Form

Participant ID (attach label below)	
Attach Participant ID label	☐ Form 01 and 02 previously submitted ☐ Form 03 #pages sent: ☐☐ • Telephone number of who to contact to process randomisation: _____ • Name of person to contact: _____ • Remember you will need the participant's NHS number.

Instructions for completing the Randomisation Request Form

1. Attach the participant's identification label in the first column.
2. In the second column: Tick to confirm that Forms 01 and 02 have previously been submitted. Tick to confirm that Form 03 is being submitted and how many pages have been sent.
3. Specify the telephone number and contact name that a member of the STOP-HCV-1 team can call to process the randomisation.

9.1.3 Randomising a participant

- Fax (0207-670-4817) or securely email (mrcctu.stophcv1@ucl.ac.uk) **Form 03 - Randomisation** to the STOP-HCV-1 Co-ordinating Centre along with a Randomisation Request Form, which should include the name and telephone number of the person at the site who will process the randomisation.
- If you have not heard back from the STOP-HCV-1 Co-ordinating Centre within 1 hour of submitting **Form 03 - Randomisation**, you should call a member of the team to ensure the randomisation form was received. The team will aim to complete randomisations as soon as possible and within an hour of receipt of a completed **Form 03 - Randomisation** (provided Form 01 and 02 were sent in advance).
- A member of the Randomisation team will call you to process the randomisation. Ensure **Form 03 – Randomisation** and the participant's NHS number are accessible as these will be required to proceed with the randomisation.
- The randomiser will go through the inclusion and exclusion criteria with you; once all answers have been confirmed and the randomiser is satisfied with the completeness of the information, the participant will be randomised. The randomiser will require the patient's NHS number to be given verbally.
- The randomisation program will verify that the eligibility criteria have been met. Once all checks are passed the randomiser will inform you of the participants randomised allocation, you should record the randomisation result on **Form 03 - Randomisation** Section F.
- After the participant has been randomised you will receive an email confirmation with the participant's enrolment number. Attached to the email will be the Participant's Individual Visit Schedule which will outline the dates in which the participant will need to attend clinic for a visit; it will also include the participant's randomisation allocation (e.g. fixed first line, no Ribavirin) and duration of treatment (e.g. 56 days). An example of a visit schedule is at the end of this chapter. The email confirmation and the visit schedule should be filed in the participant's CRF file. Also attached to the email will be the diary card specific to their randomisation allocation.
- As a default the randomisation confirmation email will be sent to PI, Lead research nurse and Trial Pharmacist at the site; you should inform the STOP-HCV-1 trial team if there are other members of the team to which the email should go.
- Discuss the randomisation allocation and visit schedule with the participant ensuring they understand how long and how often study medication should be taken for and when their next scheduled visits will be. Remind participants to take their treatment as soon as possible upon receipt and no later than 1 day after randomisation, this will allow early viral kinetics to be estimated from the Day 3 and 7 visits. We need to know as closely as possible when drugs are started so that we can estimate decays in HCV viral load at their Day 3 visit.
- Randomisation day is considered the **Day 0** visit.
- A prescription should be written for the participant's treatment allocation using the STOP-HCV-1 prescription. Prescriptions should be signed by someone designated this responsibility on the trial Signature and Delegation Log. If the patient has been

randomised to Ribavirin, please check their weight and prescribe the correct dose. Add the trial drugs prescribed to **Form 09 – Trial Drug Log**. It is advised that all participants are initially dispensed 28 days of treatment EXCEPT those randomised to 29, 30 or 31 days treatment who should be dispensed their full treatment regime on day 0.

- For participants randomised to 32-49 days treatment, pharmacy should consider setting aside the remaining balance of tablets required to make up their total allocation. The tablets should be labelled with the participant's trial number. This remaining balance should then be dispensed to the participant when they return for their day 28 visit.
- **Note:** Initially prescribing and dispensing 28 days treatment is advised due to the importance of the day 28 visit to the trial; however this decision ultimately remains at the discretion of the clinician.
- It is important to consider the visit window for the day 28 visit is +/- 1 day. It is recommended that the day 28 visit is planned on day 0. If the participant will attend this visit on day 29 then 29 days treatment will need to be dispensed.
- Discuss with the participant about events which they will be required to report to the clinical team see section 21 for event reporting criteria.
- The participant should ideally start treatment on the same day of randomisation and no later than the following day.
- Offer the participant a **Diary Card** specific to their combination regimen (tablets and OD/BD) and treatment duration to help them record pill taking. Participants should be encouraged to bring the diary card with them to each study visit. Example diary card at the end of this section. Depending on the day the participant is going to start taking the trial drug (day 0 or day 01), it may be useful to cross through a day on the diary card, if the participant starts on day 0, the last day on the diary card should be crossed through if the participant starts on day 01, day 0 should be crossed through.
- **Remind the participant that Viekirax®, Exviera®, Maviret® and Ribavirin must be taken with food.**
- **Remember to add the date of randomisation, treatment prescribed and the participant's randomisation allocation on the Screening and Randomisation Log.**
- Discuss with the participant what they should do in the event of any missed doses:

Viekirax® and Exviera®

- Participants should be instructed that if vomiting occurs within 6 hours of dosing an additional dose of Viekirax® and Exviera® should be taken. However if vomiting occurs more than 6 hours after dosing no further dosing is needed.
- If a dose of trial drug is missed, the prescribed dose can be taken within 6 hours (of usual dosing time). If more than 6 hours have passed since the drug is usually taken, the missed dose should NOT be taken and the patient should take the next dose per their usual dosing schedule. It must be made clear to participants that a double dose should not be taken. Any missed doses should be taken at the end of the treatment course.
- Example: A participant randomised to a 34 Day treatment duration routinely takes their morning dose at 8am and an evening dose at 8pm. On Day 18 the participant forgets to

take their 2 tablets of Viekirax® and 1 tablet of Exviera® and only realises this at 4pm. The participant should not take the missed dose of Viekirax® and Exviera®, but should proceed to take their evening dose of Exviera®. The missed Day 18 dose can be taken on the day after their End of Treatment (i.e. effectively day 35).

Maviret®

- Participants should be instructed that if vomiting occurs within 3 hours of dosing an additional dose of Maviret® should be taken. If vomiting occurs more than 3 hours after dosing, no further dose is needed.
- If a dose is missed and it is within 18 hours of the normal time, patients should be instructed to take the tablet as soon as possible and then patients should take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. Patients should be instructed **not to** take a double dose. Any doses missed during the treatment course should be taken at the end of the prescribed course.

Ribavirin

- Participants should be instructed that if vomiting occurs within 6 hours of dosing an additional dose of Ribavirin should be taken. If vomiting occurs more than 6 hours after dosing, no further dose is needed.
- If a dose is missed, the prescribed dose can be taken within 6 hours. If more than 6 hours has passed since their usual dosing time, the missed dose should not be taken and the participant should take their next dose as per their usual dosing schedule. Patients should be instructed not to take a double dose. The missed dose can be taken after the end of treatment visit.

Harvoni®

- Participants should be instructed that if vomiting occurs within 5 hours of dosing; an additional dose of Harvoni® should be taken. If vomiting occurs more than 5 hours after dosing, no further dose is needed.
- If a dose is missed and this is realised within 18 hours of the normal time, participants should be instructed to take the missed dose as soon as possible, patients should then take the next dose at the usual time. If it is after 18 hours then patients should be instructed to wait and take the next dose at the usual time. It should be made clear to participants that a double dose must not be taken. The missed dose can be taken after the end of treatment visit.
- Example: A participant misses their Day 44 dose of Harvoni® which they routinely take at 7am, they realise this at 6pm, and upon realising the participant should take their dose of Harvoni® and proceed to take their next dose at 7am on Day 45.

Participants should return any unused pills either directly to pharmacy, or to the trial team (who should then pass on to pharmacy). These pills will need to be counted and recorded for example on the participant accountability log or a returns log and, once destroyed, a destruction log. The destruction log should be sent to the MRC CTU.

Table 7 Summary of CRFs to be completed before and on Day 0.

CRF	Participant will be randomised	Participant will not be randomised
Form 1 - Screening	Yes	Yes
Form 2 - Laboratory Results	Yes	If results available
Form 3 - Randomisation	Yes	Yes
Form 4 - Enrolment	Yes (after randomisation)	No
Form 5 – EQ-5D	Yes (before randomisation completed by participant)	No
Form 6 – MOSCOG	Yes (before randomisation completed by participant)	No
Form 7 – SF-12	Yes (before randomisation completed by participant)	No

9.1 Day 0 Assessments

The following CRFs should be completed on Day 0:

Before randomisation: **Form 05 – EQ-5D, Form 06 – MOSCOG** and **Form 07 – SF-12.**

Post randomisation: Form 02 – Laboratory results, Form 04 – Enrolment

The following clinical information and assessments should be completed at Day 0 and reported on **Form 04 – Enrolment.**

Before Randomisation

- Medical history – Information on the participant's medical history can be obtained from the participant's medical notes or participant self-report if this is felt to be reliable. For any diagnosis, please check whether this makes the participant ineligible (e.g. Any malignancy within 5 years)
- Participants smoking status
- Details on previous HCV treatment. **Note:** previous DAA exposure for this infection is an exclusion criterion, however pegylated-interferon and/or Ribavirin is allowed.
- If the participant is a woman of child bearing potential a pregnancy test is required at Day 0. For the participant to be eligible this must be negative.
- Concomitant medication – If the participant is taking any concomitant medication this should be reported on **Form 08 - Concomitant Medication**. Any medication the

participant is currently prescribed or taking regularly without prescription should be recorded. Information for the concomitant medication log can be obtained from the participant's medical notes or from participant self-report. Nutritional supplements such as vitamins should be listed.

Post Randomisation

- 20ml whole blood for EDTA plasma storage sample
- Optional storage sample: If the participant consented to genetics sample, 2.5ml of blood must be taken at Day 0 for the PAXgene, 2.5ml of blood for EDTA DNA (if this is not taken at Day 0 is should be taken at a later visit and report on the **Form 02 – Laboratory Results** of the respective visit). If your site is participating in the collection of PBMC samples for the study, 20ml of whole blood should be collected.
- If the Participant consented to the clinic test for the IL-28 gene, the buccal sample for the POC IL28 EPISTEM test can be taken. If this is not taken at Day 0 it can be performed at a visit later visit and reported on **Form 02 – Laboratory Results** of the respective visit
- A discussion with the participant about their next visit.

Figure 5 Individual Visit Schedule

MRC Clinical Trials Unit

Individual Visit Schedule

STOP-HCV Stratified Medicine for HepC

Report run on : 01-Nov-2017 12:08

Trial number: [redacted] H551004W

Trial arm: Fixed first line, no ribavirin

Centre: 551-London, Royal London Hospital

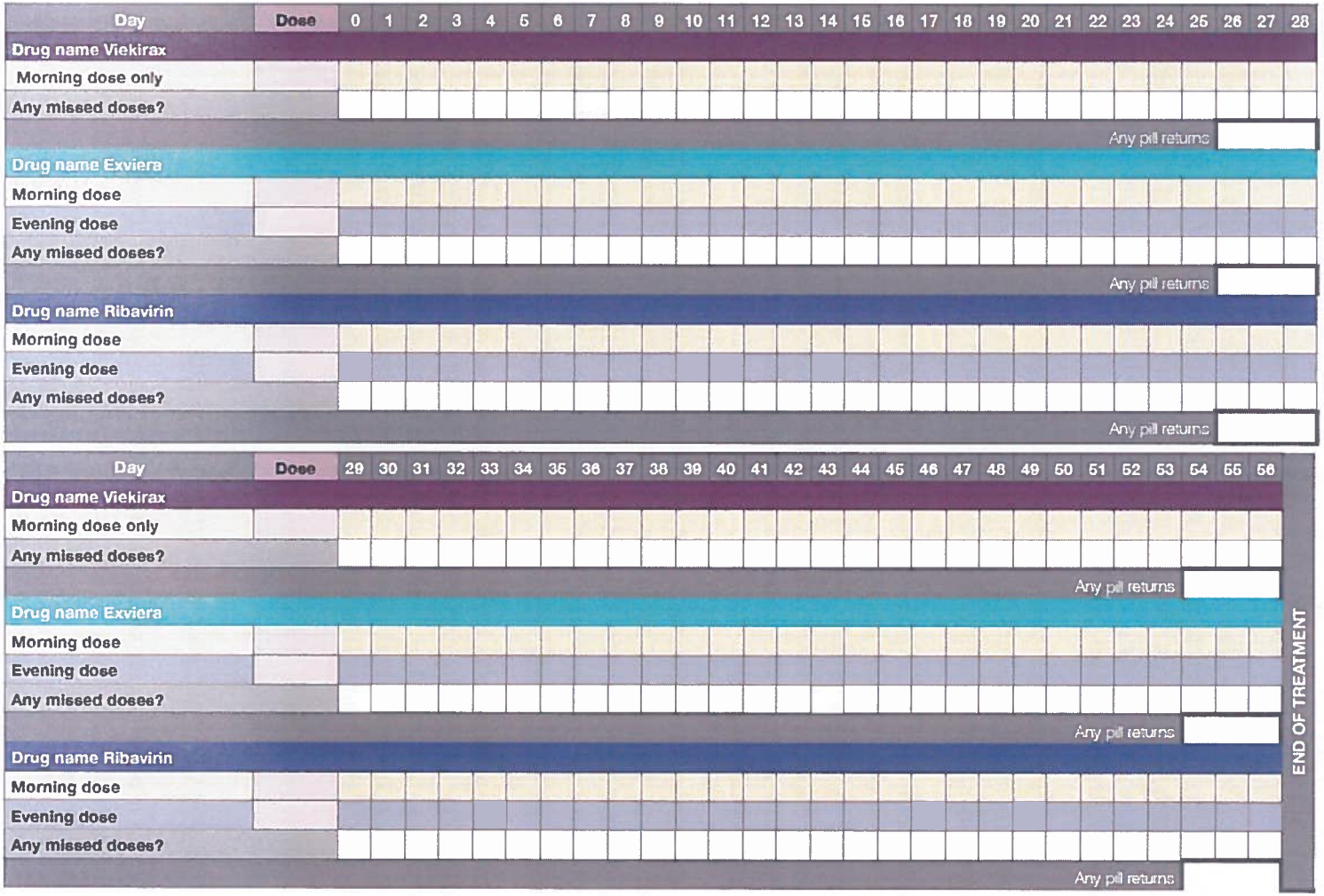
First line days: 56

Date of birth: 07 June 1990

First line treatment: Maviret (glecaprevir/pibrentasvir) - genotype 1a/1b and 4

Visit	Target Date	Actual Date	Window Open	Window Closed
Screening:Week -6		16 Oct 2017		
Enrolment:Week 0		17 Oct 2017		
First line treatment - Day 3	20 Oct 2017		19 Oct 2017	21 Oct 2017
First line treatment - Day 7	24 Oct 2017		23 Oct 2017	25 Oct 2017
First line treatment - Day 14	31 Oct 2017		30 Oct 2017	01 Nov 2017
First line treatment - Day 28	14 Nov 2017		13 Nov 2017	15 Nov 2017
First line EOT: Day 56	12 Dec 2017		09 Dec 2017	15 Dec 2017
Post EOT first line - Week 4	09 Jan 2018		06 Jan 2018	12 Jan 2018
Post EOT first line - Week 8	06 Feb 2018		03 Feb 2018	09 Feb 2018
Post EOT first line - Week 12	06 Mar 2018		03 Mar 2018	09 Mar 2018
Post EOT first line - Week 24	29 May 2018		26 May 2018	01 Jun 2018

Figure 6 Patient Diary Card – Example Viekirax, Exviera and Ribavirin 56 days



10. Follow-Up Visits & Assessments

It is important for the study that investigators and participants maintain the follow-up schedule as per the individual visit schedule report received following randomisation. The investigations specified in the protocol are required for all participants. Any additional visits or diagnostic/laboratory tests needed for patient management should occur as required at the discretion of the treating physician. Results from these investigations should be recorded on the appropriate STOP-HCV-1 follow up CRF (**Form 12 – Follow-up on treatment/EOT** or **Form 13 – Follow-up post treatment**) as unscheduled visits.

The duration of first-line treatment is determined by the participant's randomisation allocation which will be either varying or fixed duration. On both arms of the study, participants will need to attend a follow-up visit on Day 3, 7, 14 and at the End of their Treatment (EOT). Depending on the duration of the participant's treatment allocation, they may also be required to attend a visit on Day 28.

Note: If the participant has been randomised to receive 28 days treatment then the EOT visit should be completed on day 28. Those randomised to 29-31 days of treatment, should not attend a day 28 visit and instead should only attend an EOT visit.

On treatment visits should be within ±1 day of the target visit date. The day 3 visit must occur 3 or more calendar days before the day 7 visit (there should be two calendar days completely separating them). The EOT visit can be within ±3 days; however every effort should be made to schedule this on the final day of the participant's treatment allocation. Participants should continue to be followed on the same schedule even if they do not adhere to their treatment regimen.

All patients should be followed by the site clinic teams for 24 weeks after the end of first-line treatment for evaluation of virological response and any toxicity. The post EOT visits should happen within ±3 days of the target date. However, if this is not possible, a visit (with all the appropriate tests and evaluations) should still take place as soon as possible outside this window to ensure that trial outcomes are ascertained as accurately as possible in real-time.

The required assessments at all visits are the same regardless of which arm the participant is randomised to. For the specific assessments and storage samples required at each visit, please refer to **Table 1 – Trial Assessment Schedule - first-line treatment real-time tests**, **Table 2 – Sample Collection Schedule – first-line treatment sample storage** and **Table 3 – Trial Assessments and Sample Collection Schedule - Re-treatment**).

Note: At follow-up visits, if a participant is hard to bleed, the blood tests should be prioritised as follows: Biochemistry>haematology (FBC>differential>INR)>HCV viral load >storage.

The following CRFs are used to report follow-up visits:

Form 12 – Follow-up on treatment/EOT is completed for all scheduled first-line visits, re-treatment visits, EOT visits, or any unscheduled visits which occur whilst the participant is taking treatment.

Form 13 – Follow-up post treatment is completed for all scheduled first-line and retreatment visits or unscheduled visits which occur after the first-line or retreatment EOT visit.

Form 02 – Laboratory Results should also be completed for every on treatment and post treatment visit, and unscheduled visits where laboratory results are available.

As these forms are associated with multiple visits the header will need to be completed to indicate which visit is being attended. Instructions on how to complete the form headers can be found in Section 5.4.2.

As some assessments are only performed at specific visits, not all sections on the Follow-up CRF and Laboratory Results CRF need to be completed. For these sections there is guidance below the header as to which visits the section needs to be completed at. For example:

B. CLINICAL INFORMATION

Required at: First line: day 28, EOT
Retreatment: week 0, 4, 8, 12(EOT)

If there is no guidance, it means that the section should be completed at all scheduled follow-up visits.

Within sections there may also be additional directions. For example if another form needs to be completed/updated or if a question can be skipped:

A. TRIAL DRUG

1. Since the last study visit, has the participant stopped, re-started or changed dose or frequency of any trial drugs? ☐ Yes ☐ No

☞ **If yes, please record on Form 09 - Trial drug Log and submit**

The following assessments should be completed at every visit (regardless of the participant's treatment status):

Adverse events

Since the last study visit, if the participant has had any Serious Adverse events, any grade 3 or 4 events or reactions, or an adverse event of any grade leading to the modification of any trial drug (see Section 21 for event reporting criteria) then this should be recorded on **Form 12 – Follow-up on treatment/EOT** (Section C) or on **Form 13 – Follow-up post treatment** (Section B). For example:

C. ADVERSE EVENTS

1. Since the last study visit, has the participant had a serious adverse event? ☐ Yes ☐ No

☞ **If yes, please record on Form 10a- Serious Adverse Event and submit if not already sent**

2. Since the last study visit, has the participant had a non-serious but grade 3 or 4 adverse event or reaction, or an adverse event of any grade leading to modification of any trial drug? (Please ensure lab test results have been checked) ☐ Yes ☐ No

☞ **If Yes, please record on Form 11 - Non-Serious Adverse Event and submit if not already sent**

- If the event meets the serious adverse reporting criteria, then it should be reported to the STOP-HCV-1 Co-ordinating Centre within 24 hours of site awareness on **Form 10a – Serious Adverse Event**.
- All other grade 3 or 4 adverse events and reactions or an event of any grade which leads to modification of any trial drug should be reported on **Form 11 – Non-Serious Adverse Event**.
- **Form 09 – Trial Drug Log** should be updated if the event has led to a change in trial drugs.

Pregnancy

At every visit, the participant should be asked if there is any risk of pregnancy in either themselves, if a woman, or a female partner, if a man. They should be reminded of the importance of using effective contraception. Section E on **Form 12 – Follow-up on treatment/EOT** and Section D on **Form 13 – Follow-up post treatment** (see example below) should be used to report the participants pregnancy status and should be completed at first-line Day 0, Day 28, EOT, EOT+12, EOT+24 and retreatment Week 0, Week 4, EOT, EOT+12. If the participant is a woman of child-bearing potential a urine pregnancy test should be completed at these visits and the result entered under Question 2a. If the pregnancy test was not done at a required visit, the reason 'why' should be recorded in Question 2b. If the participant is male, Question 1 should always be marked 'No' and proceed to Question 4. If the participant's partner has become pregnant since their last visit the participant/partner (if present) should be provided with the Pregnant Partner Information Sheet and a **Form 10 - Serious Adverse Event** should be completed to note the event.

E. PREGNANCY

Required at: First line: day 28, EOT
Retreatment: week 0, 4, 12(EOT)

1. Is the participant a woman of childbearing potential? ☐ Yes ☐ No **If no, go to question 4**

2a. If yes, was a pregnancy test done? ☐ Yes ☐ No b. If 2a. is no, reason: _____

	Date specimen obtained	Result
3. If 2a. is yes, record the result of the urine pregnancy test: a.	d d m m m y y y y	b. ☐ Positive ☐ Negative

☞ **If positive, please record on Form 10- Serious Adverse Event and submit if not already sent**

4. Is the participant male and has their partner become pregnant since the last visit? ☐ Yes ☐ No

☞ **If yes, please provide the participant with the Pregnancy PIS and please record on Form 10- Serious Adverse Event and submit if not already sent**

Concomitant Medications

If the participant has started or stopped any concomitant medications (including any nutritional supplements and vaccinations) since the last study visit this should be reported in Section G of **Form 12- Follow-up on treatment/EOT** or Section F of **Form 13 – Follow-up post treatment** (see example below) and **Form 08 – Concomitant Medication Log** should be completed or updated.

G. CONCOMITANT MEDICATIONS

1. Since the last study visit, has the participant started or stopped taking any medications other than trial drugs? ☐ Yes ☐ No

☞ **If yes, complete Form 08 - Concomitant Medication log and submit**

Resource Utilisation

At each visit it should be checked if the participant has visited the GP, Accident and Emergency department or been admitted to hospital since their last visit. The number of visits to the above facilities should be reported in Section I of **Form 12- Follow-up on treatment/EOT** and Section H of **Form 13 – Follow-up post treatment** (see below). If the participant was admitted to hospital the date of admission and discharge should also be entered into this Section. **Note**: Unplanned inpatient hospitalisation or prolongation of hospitalisation meets the criteria for Serious Event reporting and should therefore be reported on **Form 10a – Serious Adverse Event**. It should also be checked if the participant has had any blood transfusions, scans or X-rays and if so, this should be recoded in this Section too.

I. RESOURCE UTILISATION

1. Since the last study visit how many times has the participant :
   a. Visited the GP ☐☐
   b. Visited A&E ☐☐
   c. Been admitted to hospital ☐☐

☞ **If the participant has not been admitted to hospital please move on to question 3**

2. If the patient has been admitted to hospital:

a. Date of admission	b. Date of discharge	c. Reason for admission:
d d m m m y y y y	d d m m m y y y y	
d d m m m y y y y	d d m m m y y y y	

3a. Since the last visit, how many blood transfusions has the participant had? ☐☐

If any, b. Date of transfusion: d d m m m y y y y c. Total Units ☐☐

d. Date of any second transfusion: d d m m m y y y y e. Total Units ☐☐

4a. Since the last visit has the participant had any scans or X-rays? ☐ Yes ☐ No

b. If yes, please provide details on the scan or X-ray: _____

The following assessments should be completed at every on-treatment visit:

Trial Drug Adherence

At every on-treatment follow-up visit the participant's adherence to the trial medication should be assessed since the last study visit. Adherence should be discussed with the participant and their diary card reviewed. It should be checked how often these trial drugs were taken with food since the last visit. Also if the participant has stopped, restarted or changed dose or frequency of the trial drugs should be checked since the last visit and this should be reported on **Form 12 – Follow-up on treatment/EOT,** Section A (see below). If a STOP, RESTART or CHANGE has occurred the details should also be logged on **Form 09 - Trial Drug Log** (see Section 13 on Trial Drug Log completion).

Completion of Form 12, Section A:

- If the participant has missed part of a dose (e.g. 1 pill of a 2 pill dose for Viekirax®), this should be reported as 00.5 on question 4 (Section A, Form 12).

- If the participant has missed a dose since their last visit but not within the last 7 days, the drug codes (question 3) for the trial drug the participant is taking should be entered and the number of prescribed doses over the last 7 days completed as appropriate, but the number of missed doses should be entered as '00.0'
- If the participant is not taking the specified drug prior to the visit question 7 and 8 should be completed and 'not taking' marked. Form 12, Section A:

A. TRIAL DRUG

1. Since the last study visit, has the participant stopped, re-started or changed dose or frequency of any trial drugs? ☐ Yes ☐ No

☞ **If yes, please record on Form 09 - Trial Drug Log and submit**

2. Since the last study visit, has the participant missed any doses of trial drug ? ☐ Yes ☐ No **If no, go to question 6**

If yes, since the last visit, how many doses of each prescribed trial drug has the participant missed over the last 7 days?

3. Drug Code	4. Number of Missed Doses	5. Number of Prescribed Doses over the last 7 Days
☐☐☐	missed ☐☐ • ☐	doses out of ☐☐ prescribed doses
☐☐☐	missed ☐☐ • ☐	doses out of ☐☐ prescribed doses
☐☐☐	missed ☐☐ • ☐	doses out of ☐☐ prescribed doses

Drug Codes
EXV Exviera (Dasabuvir) 14 doses in 7 days
VIK Viekirax (Ombitasvir Pantaprevir/ritonavir) 7 doses in 7 days
MVT Maviret (Glecaprevir/Pibrentasvir) 7 doses in 7 days (3 pills per dose)
RBV Ribavirin 14 doses in 7 days
HAR Harvoni (Sofosbuvir/Ledipasvir) 7 doses in 7 days

☞ **If the participant missed doses for 2 consecutive days or more, please record on Form 09 - Trial Drug Log and submit**

6. Record date and time the participant took their last pills:

a. Last once daily pill: d d m m m y y y y b. Time: h h : m m (use 24 hour clock)

c. Last twice daily pill: d d m m m y y y y d. Time: h h : m m (use 24 hour clock)

7. Prior to this visit, how often did the participant take their VIK +/- EXV or MVT doses with food?

☐ Not taking VIK +/- EXV or MVT ☐ All of the time ☐ Most of the time ☐ Some of the time ☐ None of the time

8. Prior to this visit, how often did the participant take their RBV doses with food?

☐ Not taking RBV ☐ All of the time ☐ Most of the time ☐ Some of the time ☐ None of the time

If the participant has missed doses of the trial medication for 2 consecutive days or more since their last scheduled study visit, a STOP and RESTART should be recoded on **Form 09 - Trial Drug Log.**

Note: If the participant was randomised to receive Ribavirin and there has been a change in the participant's weight since enrolment, it should be considered whether a change in Ribavirin dose is required.

Next Visit

The date of next visit should be recorded to help with the planning of on treatment visits. This should be reported on **Form 12 – Follow-up on treatment/EOT,** Section K.

The following assessments should be completed only at those visits specified in the trial assessment schedule:

Quality of Life questionnaires

The Quality of Life questionnaires (**Form 05 – EQ-5D, Form 06 – MOSCOG** and **Form 07 – SF-12)** should be completed by the participant at first-line day 0, EOT, EOT+12 and retreatment week 0, EOT, EOT+12.

Stored Samples

The volume of storage samples to be collected is dependent upon the visit attended and the sample processing route your site is using. For guidance on sample processing please refer to the appropriate Lab Manual; for **Local Processing and Storage**, **Imperial Processing and Storage, or Sites sending STOP-HCV-1 samples to HCV Research UK Biobank**.

When a storage sample has been collected for EDTA plasma at a visit, **Form 12- Follow-up on treatment/EOT** (Section H) or **Form 13 – Follow-up post treatment** (Section G) should be completed to record the size of the collection tubes, number of tubes collected, date the samples were collected and the collection time (see below for an example).

H. STORED SAMPLES

Required storage

		10ml Required	20ml Required
1. EDTA plasma	**Local/Imperial Processing:**	**First line: day 3, 7, 14, 28** **Retreatment: week 0, 2, 4, 8, 12 (EOT)**	**First line: EOT**
	DX to Glasgow:	**First line: day 3, 7, 14** **Retreatment: week 0**	

Size of collection tubes	**Number of tubes collected**	**Date specimen obtained**	**Time of collection** (use 24 hour clock)
a. ☐☐ • ☐ ml	b. ☐☐	c. ☐☐/☐☐/☐☐☐☐	d. ☐☐ : ☐☐

If your site is participating in PBMC collection and a sample was taken for processing at Day 0, then up to a maximum of 4 other time points can be collected with EOT being the most important. When a PBMC sample is collected the same details as above should be recorded.

If the EDTA DNA sample for genetic testing was not taken from a participant who consented at Day 0, the sample can be taken at any time point following Day 0. This should be recorded on the **Form 02 - Laboratory Results** associated to the appropriate visit under Section F.

POC IL28 (EPISTEM test)

If the participant consented to the POC IL28 EPISTEM test and this was not performed at Day 0 then this can be performed at any time point following Day 0. This should be recorded on the **Form 02 - Laboratory Results** associated to the appropriate visit under Section E.

10.1 On treatment Visit Assessments

For the following visits a **Form 12 – Follow-up on treatment/EOT** should be completed.

10.1.1 First line Day 03, 07 and 14

Regardless of the participant's randomisation allocation, all participants will attend a Day 03, 07 and 14 visits.

Day 03 will be the first study visit since the participant started trial medication. At this visit confirm the day that the participant started taking their treatment. Record the start date for the trial drug on **Form 09 – Trial Drug Log** and send to the STOP-HCV-1 Co-ordinating Centre.

The following clinical information and assessments are required at these visits;

- Trial Drug Adherence
- Adverse Events
- Routine blood for HCV Viral load
- Concomitant Medication
- Resource Utilisation
- Storage Sample (10ml)
- **Day 03 and Day 07 only:** PBMC Stored Sample (see above)
- **Day 14 only:** Routine bloods for Haematology and Biochemistry.

10.1.2 First line Day 28*

***Only participants randomised to 32-49 days of treatment or 56 days of treatment will attend a Day 28 visit.**

If the patient has been randomised to receive 28 days treatment then the EOT visit schedule should be completed on Day 28. Those randomised to 29-31 days of treatment, should not attend a Day 28 visit and instead should only attend an EOT visit. Please follow the EOT schedule below.

The following clinical information and assessments are required at this (Day 28) visit;

- Trial Drug Adherence
- Participant's weight
- Adverse Events
- Pregnancy Test – if WOCBP
- Routine bloods for HCV VL, Haematology and Biochemistry
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (10ml).

Note: If unable to bleed the patient at the Day 28 visit the patient should be recalled, as this is a critical visit for clinical care.

At this visit the participant should be prescribed the remainder of their first-line treatment (as per randomised allocation). If a patient previously weighing >75 kg has lost weight and falls

to more than 2.5 kg below the 75 kg body weight threshold, or similarly, a patient previously weighing <75 kg has put on weight and increases to more than 2.5 kg above the 75 kg body weight threshold at the Day 28 visit, the Ribavirin dose should be adjusted as per Protocol Section 5.5.1. If the Ribavirin dose is adjusted document the change on the **Form 09 – Trial Drug Log.**

Record on **Form 12 – Follow-up on treatment/EOT** Section J, the number of days dose the participant is prescribed and the date of their next visit.

For all participants their next visit will be their EOT visit.

10.1.3 First line End of Treatment (EOT) visit

All participants will attend an EOT visit.

The following clinical information and assessments are required at this visit;

- Trial Drug Adherence
- Participant's weight
- Adverse Events
- Pregnancy Test – if WOCBP
- Routine bloods for HCV VL, Haematology and Biochemistry
  (If HIV infected: Immunology and HIV VL)
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (20ml)
- PBMC Stored Sample (see above)
- Quality of Life Questionnaires.

Note: If unable to bleed the patient at the EOT visit the patient should be recalled, as this is a critical visit for clinical care.

Once the participant has finished their randomisation allocation and their last dose of trial medication has been taken **Form 09 – Trial Drug Log** should be updated to report a STOP and sent to the STOP-HCV-1 Co-ordinating Centre.

10.2 Post End of First line Treatment Visit Assessments

For the following visits a **Form 13 – Follow-up post treatment** should be completed.

10.2.1 First line Post EOT +04, +08

The following clinical information and assessments are required at these visits;

- Adverse Events
- Routine bloods for HCV VL
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (**EOT+04** and **EOT+08** - 10ml)
- For sites sending samples via Glasgow DX: Storage Sample (**EOT+04** - 10ml)
- **EOT+04 only:** Participant's weight
- **EOT+04 only:** PBMC Stored Sample (see above).

10.2.2 First line Post EOT +12, +24

The following clinical information and assessments are required at these visits;

- Participant's weight
- Adverse Events
- Pregnancy Test – if WOCBP
- Routine bloods for HCV VL, Haematology and Biochemistry (**EOT+24 only:** If HIV infected: Immunology and HIV VL)
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (**EOT+12** – 20 ml, **EOT+24** – 10ml)
- **EOT+12 only:** Quality of Life Questionnaires.

Note: If unable to bleed the patient at the post EOT+12 visit the patient should be recalled, as this is a critical visit for clinical care.

11. Treatment Failure

Failure of first-line treatment is defined in the approved protocol as:

i. two consecutive measurements of HCV RNA >LLOQ (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ at any time, with the latter confirmatory measurement also being >2000 IU/ml

or

ii. two consecutive measurements of HCV RNA (taken at least one week apart) that are >1 $\log_{10}$ increase above HCV RNA nadir on treatment and >2000 IU/ml at any time.

Therefore any patient with a single HCV RNA > LLOQ after two consecutive HCV RNA < LLOQ, or with a single value > 2000 IU/ml and > 1 log10 increase above the HCV RNA nadir during or post end of treatment should be recalled for a second HCV RNA test at least one week after the initial values to confirm whether failure has occurred, see appendix 1 for further guidance on determining the criteria a participant meets for Treatment Failure.

Upon receiving a confirmatory HCV VL result **which must always be above 2000 IU/ml,** immediately complete **Form 14 - Treatment Failure** and send to the STOP-HCV-1 Co-ordinating Centre with:

a. A de-identified copy of the confirmatory HCV VL lab report - with PID label attached.
b. A list of the HCV VL throughout the trial

On the **Form 14-Treatment Failure** you should indicate on the form which failure criteria the participant meets as per the above definitions and provide a date and result of the confirmatory viral load. If this is the participant's first treatment failure, and the participant will be offered retreatment (as per the protocol), specify when the planned re-treatment start date is. The CRF also asks your opinion on if a) incomplete adherence and/or b) adverse events have had a role in the treatment failure; if you believe there is another reason for the failure, indicate "other" and specify in the space provided.

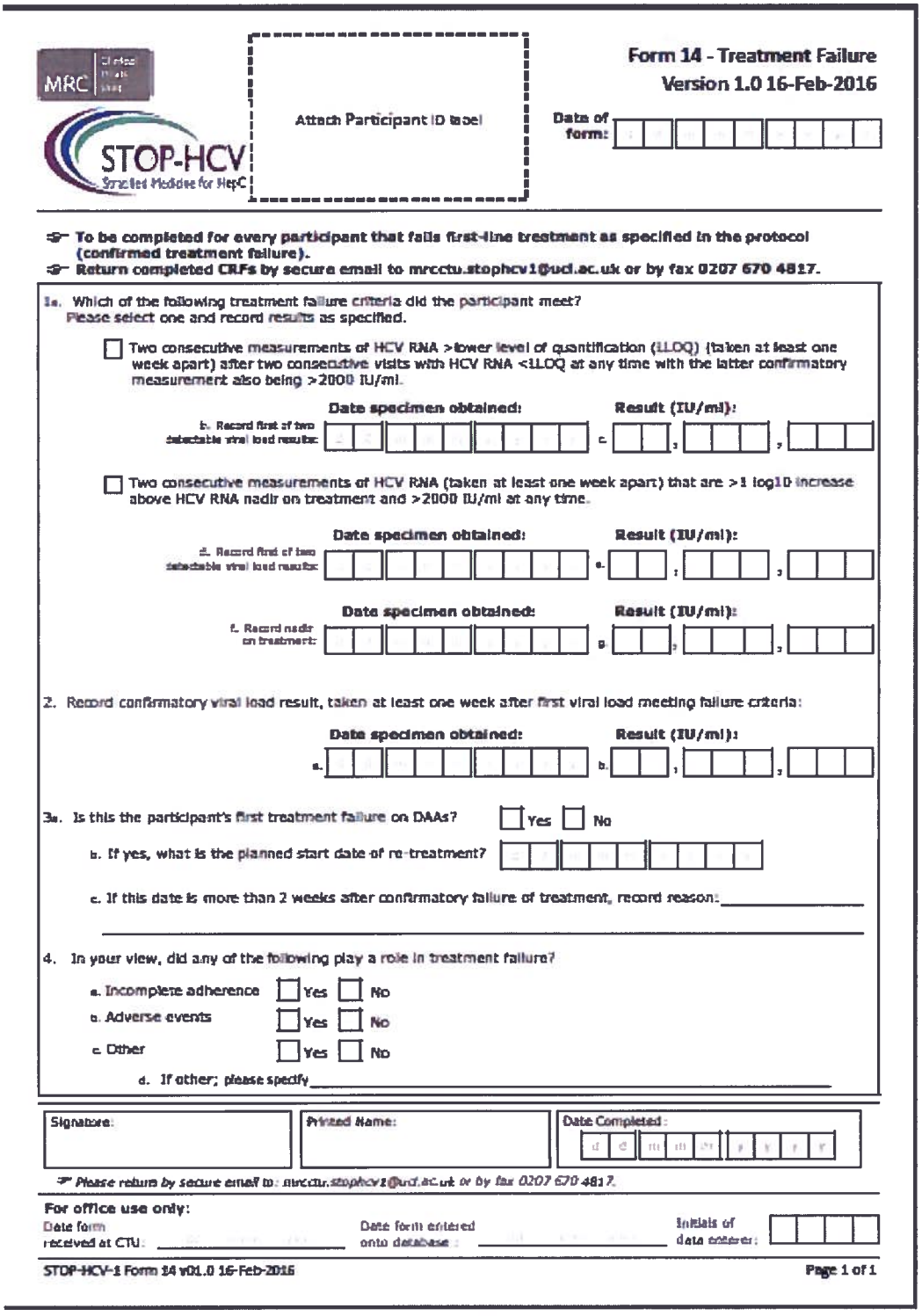
The STOP-HCV-1 Co-ordinating Centre will process the Form 14 - Treatment Failure within 24 hours of receipt. An email will be sent to you to confirm the participant meets the treatment failure criteria and the Retreatment Visit Schedule will be attached.

Only after email confirmation from the STOP-HCV -1 Co-ordinating Centre should the participant commence retreatment.

If a participant is confirmed to have failed first-line treatment they should move on to the retreatment schedule (**Table 3 – Trial Assessments and Sample Collection Schedule - Re-treatment**). See section 12 for details on retreatment visits and assessments.

If the participant fails retreatment; subsequent treatment in the event of overall failure will be at the discretion of the responsible physician and availability of new treatment regimens through NHS commissioning.

Figure 8 Form 14 – Treatment Failure



MRC Clinical Trials Unit

STOP-HCV Stratified Medicine for HepC

Attach Participant ID label

Form 14 - Treatment Failure
Version 1.0 16-Feb-2016

Date of form: d d m m m y y y y

☞ **To be completed for every participant that fails first-line treatment as specified in the protocol (confirmed treatment failure).**
☞ **Return completed CRFs by secure email to mrcctu.stophcv1@ucl.ac.uk or by fax 0207 670 4817.**

1a. Which of the following treatment failure criteria did the participant meet?
Please select one and record results as specified.

☐ Two consecutive measurements of HCV RNA >lower level of quantification (LLOQ) (taken at least one week apart) after two consecutive visits with HCV RNA <LLOQ at any time with the latter confirmatory measurement also being >2000 IU/ml.

	Date specimen obtained:	Result (IU/ml):
b. Record first of two detectable viral load results:	d d m m m y y y y	c. , ,

☐ Two consecutive measurements of HCV RNA (taken at least one week apart) that are >1 log10 increase above HCV RNA nadir on treatment and >2000 IU/ml at any time.

	Date specimen obtained:	Result (IU/ml):
d. Record first of two detectable viral load results:	d d m m m y y y y	e. , ,
f. Record nadir on treatment:	d d m m m y y y y	g. , ,

2. Record confirmatory viral load result, taken at least one week after first viral load meeting failure criteria:

	Date specimen obtained:	Result (IU/ml):
	a. d d m m m y y y y	b. , ,

3a. Is this the participant's first treatment failure on DAAs? ☐ Yes ☐ No

b. If yes, what is the planned start date of re-treatment? d d m m m y y y y

c. If this date is more than 2 weeks after confirmatory failure of treatment, record reason: _____

_____

4. In your view, did any of the following play a role in treatment failure?

a. Incomplete adherence ☐ Yes ☐ No
b. Adverse events ☐ Yes ☐ No
c. Other ☐ Yes ☐ No
d. If other; please specify _____

Signature:	Printed Name:	Date Completed: d d m m m y y y y

☞ *Please return by secure email to: mrcctu.stophcv1@ucl.ac.uk or by fax 0207 670 4817.*

For office use only:
Date form received at CTU: _____ Date form entered onto database: _____ Initials of data entryer: _____

STOP-HCV-1 Form 14 v01.0 16-Feb-2016 Page 1 of 1

12 Re-treatment Visit Assessments

Patients who fail on or after first-line treatment will be treated with 12 weeks of Harvoni® plus Ribavirin as soon as possible (but taking into consideration the wishes of the participant). See Section 11 for definitions of treatment failure within the trial. Participants will have the following visits after starting retreatment: Week 0, 2, 4, 8 and 12 (EOT); then post EOT Weeks: 4, 8, 12, and 24.

Once a **Form 14 - Treatment Failure** has been received at the STOP-HCV-1 Co-ordinating Centre and it is confirmed the participant meets the treatment failure criteria a Retreatment Visit Schedule will be generated using the planned start date of re-treatment (**Form 14 – Treatment Failure**, Question 3b). If the planned start date changes and you would like an updated Retreatment Visit Schedule prior to the participant attending their first retreatment visit, please update the planned start date and send the updated form to the STOP-HCV-1 Co-ordinating Centre. A new schedule will be generated and sent to you. Once the Week 0 visit has been attended, the Retreatment Visit Schedule will be updated to represent the correct visit windows following Week 0. If this schedule is different from the windows previously generated using the planned date, the updated visit schedule will be sent to you.

Alongside the Retreatment Visit Schedule the STOP-HCV-1 Co-ordinating Centre will send a diary card for 12 weeks of Harvoni® and Ribavirin to be offered to the participant when starting treatment.

The visit windows for retreatment are also ±1 day of the target date for on treatment and EOT visits; and ±3 days of the target date for post treatment visits.

Reminder: Ensure the participant has been registered on Blueteq for retreatment completing a STOP-HCV-1 Retreatment Blueteq form.

12.1 Retreatment On-treatment Visit Assessments

For the following visits a **Form 12 – Follow-up on treatment/EOT** should be completed.

12.1.1 Retreatment Week 0

Participants should attend clinic for the start of retreatment.

Note: If the following laboratory tests: haematology, biochemistry, coagulation markers, HCV viral load and CD4 count (for HIV infected participants) and plasma for storage, have already been taken from the participant within the 7 days prior to the planned retreatment start day (as part of the participant's first line schedule) they do not need to be repeated at the start of retreatment. Otherwise they should be done at this visit.

The following clinical information and assessments are required at this visit;

- Participant's weight
- Adverse Events
- Pregnancy Test – if WOCBP
- Routine bloods for HCV VL, Haematology, Biochemistry and Coagulation Markers

(If HIV infected: Immunology and HIV VL)
- Concomitant Medication
- Resource Utilisation
- Storage Sample (10ml)
- Quality of Life Questionnaires.

Note: When completing Form 12, Section A, for the Trial Drug Adherence, Question 1 should be marked 'no' as the participant is starting a new treatment course rather than re-starting the previous treatment course.

A prescription should be written for the participant's retreatment medication using the STOP-HCV-1 prescription. Prescriptions should be signed by someone designated this responsibility on the trial Signature and Delegation Log. Add the participant's retreatment regimen to the **Form 09 - Trial Drug Log**. Participants should only be prescribed treatment on a 4 weekly basis.

12.1.2 Retreatment Week 02

The following clinical information and assessments are required at this visit;

- Trial Drug Adherence
- Adverse Events
- Routine bloods for HCV VL, Haematology and Biochemistry
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (10ml).

This visit will be the first study visit since the participant started retreatment medication. At this visit confirm the day that the participant started taking their treatment and record the start date for the trial drug on **Form 09 – Trial Drug Log** and send to the STOP-HCV-1 Co-ordinating Centre.

12.1.2 Retreatment Week 04 and Week 08

The following clinical information and assessments are required at these visits;

- Trial Drug Adherence
- Participant's weight
- Adverse Events
- Routine bloods for HCV VL, Haematology and Biochemistry
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (10ml)
- **Week 04 only:** Pregnancy Test – if WOCBP

Note: If a patient previously weighing >75 kg has lost weight and falls below the 75 kg body weight threshold, or similarly, a patient previously weighing <75 kg has put on weight, the Ribavirin dose should be adjusted as per Protocol Section 5.5.1. If the Ribavirin dose is adjusted document the change on the **Form 09 – Trial Drug Log.**

At both visits the participant should be given a new prescription of study medication.

12.1.2 End of Retreatment (EOT) (Week 12)

The following clinical information and assessments are required at this visit;

- Trial Drug Adherence
- Participant's weight
- Adverse Events
- Pregnancy Test – if WOCBP
- Routine bloods for HCV VL, Haematology and Biochemistry (If HIV infected: Immunology and HIV VL)
- Concomitant Medication
- Resource Utilisation
- Storage Sample (10ml)
- Quality of Life Questionnaires.

Once the participant's last dose of trial medication has been taken **Form 09 – Trial Drug Log** should be updated.

12.2 Follow-up Visits Post End of Retreatment Treatment

For the following visits a **Form 13 – Follow-up post treatment** should be completed.

12.2.1 RetreatmentPost EOT +04, +08

The following clinical information and assessments are required at these visits;

- Adverse Events
- Routine bloods for HCV VL
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (10ml)
- **EOT+04 only:** Participant's weight.

12.2.2 RetreatmentPost EOT +12, +24

The following clinical information and assessments are required at these visits;

- Participant's weight
- Adverse Events
- Routine bloods for HCV VL, Haematology and Biochemistry(**EOT+24 only:** If HIV infected: Immunology and HIV VL)
- Concomitant Medication
- Resource Utilisation
- For sites processing samples locally or via Imperial: Storage Sample (**EOT+12** and **EOT+24** - 10ml)
- **EOT+12 only** Quality of Life Questionnaires
  EOT+12 and EOT+24 only Pregnancy Test – if WOCBP.

13. Trial Drug Log Completion

The **Form 09 - Trial Drug Log** should be used to capture the following information concerning trial drugs throughout the trial:

- Changes to drug dose or frequency
- Start of drug
- Stop of drug for 2 consecutive days or more.

Once the header has been completed the form consists of the table below (Figure 9).

Instructions on how to complete the log

- At randomisation the participant will be allocated to fixed or varying duration of First line treatment with or without Ribavirin. The trial drug log should initially be completed at the day 3 follow-up visit. This is to capture the day the participant started the trial drug rather than the day the drug was prescribed, in most cases this is likely to be the same day.
- In column 'a' the drug should be recorded using the three letter code found in the 'Drug Codes' chart below the table.
- In column 'b' record the action taken for this drug; this can only be START, STOP or CHANGE. Please note that if the participant is changing dose or frequency, START or STOP should not be used, this situation should be indicated by using the CHANGE code.
- Column 'c' should only be completed if column 'a' is Ribavirin (RBV), in the space provided enter the total daily dose of Ribavirin. If this row is for EXV, VIK, MVT or HAR leave this question blank.
- Column 'd' should only be completed if column 'a' is EXV, VIK, MVT or HAR, in the space provided enter the total number of pills per day the participant is taking. If the row is for RBV leave this question blank.
- In column 'e' enter the date the action was carried out. This should be the date the change/start/stop was carried out by the participant not the date the change was prescribed by the clinician.
- In column 'f' the reason for change should be entered using the codes in the 'Main Reason for Action' chart below the table.
- Column 'g' is a free text for any extra information regarding the reason the action has been taken. If 'f' has been marked 4 (patient directed), 5 (Adverse event) or 7 (Other) it is necessary to add extra information related to the reason.
- Once the row has been completed the person completing the entry should initial and date in the last column.
- The log should be updated every time the site becomes aware of a STOP/START/CHANGE of drug.
- When all rows have been completed, begin a new form and enter the page number as 02 and so on.
- Submit to the STOP-HCV-1 Co-ordinating Centre after any new entries are made.

The **Form 9 – Trial Drug Log** should be updated when a participant has stopped or missed taking trial drug for **2 consecutive days** or more. To document this; A row should be completed for each trial drug the participant was prescribed that was missed to record the date the participant stopped taking the trial drug, column 'b' should be completed as a STOP. When the participant restarts the trial drug a separate row should be completed for each trial drug restarted and column 'b' completed as a START to record the date the participant restarted treatment. For both STOP and START rows completed for the missed trial drug the main reason for action (column 'f') should be completed as either action 2 (Drug lost/ran out) or 4 (Patient) and extra information should be given in column 'g'.

Figure 9 Trial Drug Log

MRC UCL

STOP-HCV
Stratified Medicine for HepC

Attach Participant ID label

Form 09 - Trial Drug Log
Version 4.0 01-Nov-2017

Randomisation Date: dd / mmm / yyyy

Page number:

Start a new page when necessary.

- **Record trial drugs from enrolment and update during the trial.**
- **A "STOP" should be reported if a participant stopped taking trial drug for 2 consecutive days or more.**
- **START and STOP should not be used together for changes to dose or frequency - use CHANGE instead.**
- **A change in both dose and frequency should be reported as one CHANGE on the same row.**
- **Please return by secure email to mrcctu.stophcv1@ucl.ac.uk or by fax 0207 670 4817 after every new entry.**

Row #	a. Drug Code (see codes below)			b. Type of Action (see codes below)	c. Total Daily RBV Dose (mg)	d. Total Daily No. Pills (EXV/ VIK/HAR/ MVT)	e. Date of Action dd/mmm/yyyy	f. Main Reason (see codes below)	g. Extra Information	Initials and Date dd/mmm/yy
/	R	B	V	START	1200		03 OCT 2015	1		MG 04-Oct-15
/	R	B	V	CHANGE	600		23 DEC 2015	5	Anaemia	MG 24 Dec 15
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										
11										

Drug Codes
EXV Exviera (Dasabuvir) (250 mg)
VIK Viekirax (Ombitasvir/Paritaprevir/Ritonavir) (12.5/75/50 mg)
MVT Maviret (Glecaprevir/Pibrentasvir) (100/40 mg)
RBV Ribavirin
HAR Harvoni (Sofosbuvir /Ledipasvir) (400/90 mg)

Type of Action
START
STOP
CHANGE (change of dose and/or frequency)

Main reason for Action
1=Start/restart
2=Drug lost/ran out
3=Hepatitis C treatment failure
4=Patient (describe in Extra Information)
5=Adverse event (describe in Extra Information)
6=End of Treatment (EOT)
7=Other (describe in Extra Information)

For office use only:
Date form received at CTU: dd - mmm - yyyy
Date form entered onto database: dd - mmm - yyyy
Initials of data enterer:

STOP-HCV-1 Form 09 v4.0 01-Nov-2017

14. Concomitant Drug Log Completion

Form 08 - Concomitant Medication Log should initially be completed at enrolment with any medications other than trial drug the participant is prescribed or taking regularly without prescription. The log should then be updated continuously throughout the trial to track when the participant begins new concomitant medications or stops taking medication that is already logged. This includes nutritional supplements and vaccinations. Once the header has been completed the form consists of the table below (Figure 10).

Instructions on how to complete the log

- In column 'a' write the concomitant medication's drug name; only one medication should be entered per row.
- In column 'b' enter the date the participant started taking the medication. Once these have been filled the person completing the entry should initial and date in the fourth column.
- If the participant stops taking the medication during the trial, the date stopped should be entered into column 'c' and the final column initialled and dated by the person completing the entry.
- When all the rows have been filled, begin a new form to record further additions with the page number entered as 02 and so on.
- Submit to the STOP-HCV-1 Co-ordinating Centre after any new entries are made.

Figure 10 Concomitant Medication Log

Row #	a. Medication	b. Date started dd/mmm/yyyy								Initials and Date dd/mmm/yy	c. Date stopped dd/mmm/yyyy								Initials and Date dd/mmm/yy
/	Influenza vaccination	0	3	0	C	T	2	0	1	1	MC 04 Oct 11	0	3	0	C	T	2	0	1	1	MC 04 Oct 11
/	Ginkgo supplement	2	6	J	U	N	2	0	1	2	MC 10-Jun-12	1	5	A	U	G	2	0	1	2	MC 16-Aug-12
1																					
2																					
3																					
4																					
5																					
6																					
7																					
8																					
9																					
10																					

15. Missed Visits

If a participant misses any scheduled appointments after randomisation, a minimum of 3 attempts must be made to contact and locate the participant. An entry should be made in the notes to document that contact has been attempted. The **Form 15 – Missed Visit Log** should be completed.

Figure 11 Form 15 - Missed Visit Log

MRC Clinical Trials Unit

STOP-HCV Stratified Medicine for HepC

Attach Participant ID label

Page number ☐☐ Start a new page when necessary.

Randomisation Date: d d m m m y y y y

Form 15 - Missed Visit Log
Version 0.3 25-Jan-2016

- **Record when a participant misses any scheduled appointment after randomisation through to the scheduled final visit date.**
- **At least 3 attempts must be made to contact and locate a patient following each missed visit and attempts documented in patient records**

1. Date of missed scheduled visit	2. Visit missed	3. Were at least 3 attempts at contact made?	4a. Was a new appointment made?	5a.Comments; include reason for missed visit if known	Initials And Date dd/mmm/yyyy
d d m m m y y y y	First line: Day ☐☐ EOT ☐ EOT+week ☐☐ / Retreatment: Week ☐☐ EOT ☐ EOT+week ☐☐	☐Yes ☐ No	☐Yes ☐ No	☐Forgot appointment ☐Work-related or family related commitments ☐Intercurrent illness ☐Other, b.Please specify: ______	
d d m m m y y y y	First line: Day ☐☐ EOT ☐ EOT+week ☐☐ / Retreatment: Week ☐☐ EOT ☐ EOT+week ☐☐	☐Yes ☐ No	☐Yes ☐ No	☐Forgot appointment ☐Work-related or family related commitments ☐Intercurrent illness ☐Other, b.Please specify: ______	
d d m m m y y y y	First line: Day ☐☐ EOT ☐ EOT+week ☐☐ / Retreatment: Week ☐☐ EOT ☐ EOT+week ☐☐	☐Yes ☐ No	☐Yes ☐ No	☐Forgot appointment ☐Work-related or family related commitments ☐Intercurrent illness ☐Other, b.Please specify: ______	
d d m m m y y y y	First line: Day ☐☐ EOT ☐ EOT+week ☐☐ / Retreatment: Week ☐☐ EOT ☐ EOT+week ☐☐	☐Yes ☐ No	☐Yes ☐ No	☐Forgot appointment ☐Work-related or family related commitments ☐Intercurrent illness ☐Other, b.Please specify: ______	
d d m m m y y y y	First line: Day ☐☐ EOT ☐ EOT+week ☐☐ / Retreatment: Week ☐☐ EOT ☐ EOT+week ☐☐	☐Yes ☐ No	☐Yes ☐ No	☐Forgot appointment ☐Work-related or family related commitments ☐Intercurrent illness ☐Other, b.Please specify: ______	

Keep this Form in the participant's study file as a cumulative clinic record. Every time a new record is made, initial and date the record in the columns provided and return by secure email to mrcctu.stophcv1@ucl.ac.uk

Instructions on how to complete the log

- In column '1' enter the date of the missed scheduled visit.
- In column '2' mark which study visit has been missed. Specify the day or week number of the visit, or tick the EOT box.
- In column '3' confirm if 3 attempts of contact have been made by marking "yes" or "no".
- If contact has been made with the participant, mark if a new appointment has been made in column '4a' and provide a reason for missing the initial scheduled visit in column '5a'.
- The person making the entry should initial and date the entry in the final column.
- Submit to the STOP-HCV-1 Co-ordinating Centre after any new entries are made.

Participants will be classified as "lost to follow-up" if they have not been seen at the final EOT + 24 week within a [-6,+6] week window.

16. Participant payments

The trial will provide £10 towards the cost of travel to the clinic for each of the following 3 first line visits considered additional to standard treatment:

- Day 3
- Day 7
- Day 28

If re-treatment is required, £10 will also be provided for each of the retreatment visits.

This money will be included in the main site payments and sites should follow local procedures for paying study participants this money.

17. Point of Care IL28 polymorphism (EPISTEM) test

- The EPISTEM test can be performed at any study visit following consent to the trial. Upon request by the participant, you may feedback their result to them. The importance of the participant continuing with their randomised allocation and prescribed treatment, regardless of the result, should be made clear.
- The STOP-HCV-1 Co-ordinating Centre will provide all equipment and train sites on performing the EPISTEM test. Instruction leaflets are also available; please contact the trial team if you would like these sent to you.
- If any problems arise with the equipment, please contact the STOP-HCV-1 Co-ordinating Centre. If the machine is showing an error message, it is useful to take a photo and include this in the email explaining the problem.

18. Participant Withdrawals

Participants may cease their randomised trial drugs at any time, and/or refuse retreatment. This is not participant withdrawal. Providing they are willing (see below), these patients should continue to be followed up "off study drug, on study" until the primary endpoint time of (originally planned) EOT+12 weeks. If they stop very shortly after randomisation additional visits that would have occurred on treatment may be missed, but EOT+4, EOT+8 and EOT+12 week visits should occur as scheduled wherever possible.

Participants should be encouraged not to leave the whole trial. If they do not wish to remain on trial follow-up however, their decision must be respected and the patient will be withdrawn from the trial. In this situation, the patient should be asked whether or not they are willing to provide follow-up through routine electronic records (that is, not to attend study-specific visits but to allow data collected within the NHS for routine care to be used for trial comparisons).

The STOP-HCV-1 Co-ordinating Centre should be informed of the patient's decision regarding withdrawal (no further data of any kind, or follow-up through electronic medical records) in writing clearly indicating the participant's trial number and their reason for withdrawal. Prior to withdrawing from the trial, the patient will be asked to have assessments performed as appropriate for the primary endpoint EOT+12 week visit although they would be at liberty to refuse any or all individual components of the assessment.

If a participant withdraws from the trial, the medical data collected during their previous consented participation in the trial will be kept and used in analysis. Consent for future use of stored samples already collected can be refused when leaving the trial early (but this should be discouraged and should follow a discussion). If consent for future use of stored samples already collected is refused, then all such samples will be destroyed following the procedures of the institution where the samples reside at the time (local or central storage).

If a participant withdraws from the trial this should be recorded on **Form 16 – Participant Status**. Section A and section B should be completed.

Patients may change their minds about stopping trial follow-up at any time and re-consent to participation in the trial, including taking repeat samples.

Participants who stop trial follow-up early will not be replaced, as the total sample size includes adjustment for losses to follow-up.

19. Participant Transfers

A participant may wish to transfer their care to another clinic, for example following a move. Where possible we would like to encourage participants to continue on the trial and move their trial study visits to another STOP-HCV-1 site.

The STOP-HCV-1 Co-ordinating centre should be informed of any possible transfers, who will be able to inform you of other possible STOP-HCV-1 trial sites that the participant may be able to transfer to.

It will not always be possible for a participant to transfer due to funding and study payments; however every effort will be made to come to an agreement between two sites to facilitate a transfer.

If a transfer is agreed, this should be recorded on **Form 16 – Participant Status**. Section A and Section C should be completed.

Prior to the participant transferring, the original site should ensure all outstanding queries are resolved. The STOP-HCV-1 Co-ordinating Centre will put the two sites in contact so that the participant's name, contact details and medical summary can be sent on to the new site. **The STOP HCV-1 Co-ordinating Centre should not be copied in to any correspondence containing participant identifiable information.**

The STOP-HCV-1 Co-ordinating Centre will provide the new site with the participant's individual visit schedule and new PID and specimen labels.

The participant will need to sign consent at the new site. The STOP-HCV-1 Co-ordinating Centre should be informed on the date when the new consent is signed. At this point the participant will be officially transferred over to the new site. All existing queries will also transfer over to the new site which is why it is important for these to be resolved by the original site prior to transfer.

20. Participant Death

If a participant dies whilst enrolled on the trial, this should be reported as a serious adverse event on **Form 10a – Serious Adverse Event** within 24 hours of site awareness.

The death should also be recorded on **Form 16 – Participant Status**. Section A and section D should be completed.

21. Safety Management & Reporting

21.1 Event Definitions

Table 8 Event Definitions

TERM	DEFINITION
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant to whom a medicinal product has been administered including occurrences that are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Summary of Product Characteristics (SPC) or Investigator Brochure (IB) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: Results in death Is life-threatening* Requires hospitalisation or prolongation of existing hospitalisation** Results in persistent or significant disability or incapacity Consists of a congenital anomaly or birth defect Is another important medical condition***

* The term life-threatening in the definition of a serious event refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe, for example, a silent myocardial infarction.

** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, that has not worsened or for an elective procedure do not constitute an SAE.

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. The following should also be considered serious: important AEs or ARs that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above; for example, a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not result in hospitalisation or development of drug dependency.

21.1.1 Serious Adverse Events (SAE)

The following important events, as per table 8, are considered **Serious Adverse Events** and must be reported to the STOP-HCV-1 Co-ordinating Centre **within 24 hours** of site awareness. This is to meet guidance from the European Commission's "Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use (CT-3) (2011/C 172/01) guidelines":

- Events resulting in Death
- Events that are Life threatening
- Events requiring inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability / incapacity
- Congenital anomaly/birth defect
- Other important medical condition/event*

See notes under table 8 for definitions of life-threatening and hospitalisations.
It is important that these events are reported promptly to ensure participant safety.

A source of confusion in clinical trials can be the difference between a "**severe** adverse event" and a "**serious** adverse event (SAE)".

"Severity" refers to the grade of the event, which is a rating of how abnormal an AE is. Grade 3 is termed "severe" and grade 4 "life-threatening". However a grade 4 AE does not necessarily mean that the participant is at a real, not hypothetical, risk of death which is the definition of life-threatening used to define a serious adverse event.

AEs can be "severe" but not "serious" – e.g. isolated highly raised but asymptomatic LFTs would be a grade 4 AE (based on toxicity criteria) that should not be reported as an SAE (because it does not carry a real, not hypothetical risk of death).

Not being an SAE does not mean that the event is not important; grade 3 and 4 AEs should still be reported on **Form 11 - Non-serious Adverse Event**.

21.1.2 *Notable Event – Pregnancy

- Pregnancies that occur during the trial, either in a patient or in a female partner of a male patient (with their specific consent) will be reported as an SAE during the active phase of follow-up.
- All female patients should be followed for at least 4 months (16 weeks) as part of the trial follow-up schedule (to 24 weeks post EOT).
- Pregnancies in the female partners of male patients will be ascertained at the EOT+24 week visit and at the patients next routine clinic visit outside the trial (to cover the 7 month cut-off for Ribavirin exposure in male patients).
- Information on pregnancy outcome will be reported to the MHRA. Although it is unknown to what extent Ribavirin is excreted in breast milk, the SPC recommends avoiding breast-feeding during Ribavirin receipt.

- See further guidance on the management of pregnancy in section 21.6 below.

21.1.3 Adverse Events (AEs)

Examples of adverse events include:

- an exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event or condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or a symptom present at baseline that worsens following administration of the study treatment

Safety laboratory assessments will be performed in the trial and sites are asked to review clinical AEs and SAEs at each participant's visit particularly in relation to their relationship with study medications. All HCV-related events which meet the above definition should be reported as an Adverse Event.

Laboratory abnormalities (clinical chemistry and haematology) that require medical or surgical intervention or lead to an interruption, modification or discontinuation of study medication will be recorded as an AE or a SAE if they meet the SAE reporting criteria above.

In addition, laboratory or other abnormal assessments (e.g. electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE.

Laboratory abnormalities in the absence of clinical symptoms should not be reported as a SAE.

Procedures must not be reported as serious adverse events, instead the condition or the diagnosis leading to the procedure is the event, if it meets reporting criteria as a serious adverse event.

21.1.4 Adverse Reactions (AR)

Adverse reactions include any untoward or unintended response to drugs. Grade 3 or 4 reactions to the trial drug should be reported as an AE or, if they meet the SAE reporting criteria, a SAE. Any reactions that lead to a modification in trial drug administration should be reported regardless of the grade.

21.1.5 Discontinuation of study medication due to an AE/SAE

Any participant experiencing an AE or SAE should be followed up until the resolution of the event. If a participant experiences an AE or SAE which leads to their discontinuation of study medication they should continue to be followed up as "off study drug but on study".

If a participant wishes to withdraw from study visits after an AE/SAE which lead to a discontinuation of study medication the participant should be followed up in routine clinic (outside of the trial) for 12 weeks following cessation of therapy.

21.2 SAE and Non-SAE Reporting Requirements and Procedures

21.2.1 SAEs

Serious adverse events should be reported to the STOP-HCV-1 Co-ordinating Centre by secure email mrcctu.stophcv1@ucl.ac.uk or by fax to **0207-670-4817** within 24 hours of site awareness on **Form 10a – Serious Adverse Event.**

21.2.2 Investigator Responsibilities

Investigators should notify the STOP-HCV-1 Co-ordinating Centre of all SAEs occurring from the time of randomisation until last follow-up. SARs and SUSARs must be notified to the STOP-HCV-1 Co-ordinating Centre until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system. The STOP-HCV-1 Co-ordinating Centre will notify the sponsor of any SUSARs and safety issues.

21.2.3 Assessment of Seriousness

When an AE or AR occurs, the PI or designated Sub-investigator responsible for the care of the patient must assess whether or not the event is serious using the definitions in table 9. If the event is serious then **Form 10a – Serious Adverse Event** should be complete and submitted to the trial team within 24 hours of the site becoming aware of the event.

21.2.4 Assessment of severity or grading of adverse events

The severity of all AEs and/or ARs (serious and non-serious) in this trial should be graded using the toxicity grading in the International GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities.

Link to International GSI grading table:
(http://rsc.tech-res.com/document/safetyandpharmacovigilance/table_for_grading_severity_of_adult_pediatric_adverse_events.pdf).

21.2.5 Assessment of Event Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in the below table 9. There are five categories: unrelated, unlikely, possible, probable, and definitely related. If the causality assessment is unrelated or unlikely to be related, the event is classified as an SAE. If the causality is assessed as possible, probable or definitely related, then the event is classified as an SAR.

Table 9 Assigning Type of SAE through Causality

RELATIONSHIP	DESCRIPTION	SAE TYPE
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest that there is a causal relationship (for example, the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (for example, the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (for example, because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (for example, the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered related to the trial treatment and drug is stopped or the dose is modified refer to the STOP-HCV-1 protocol for dose modification, interruption & discontinuation guidance for each of the study IMP under sections 5.3.5 (Viekirax® and Exviera®) , 5.4.5 (Harvoni®) 5.5.5 (Maviret) and 5.6.5 (Ribavirin).

21.2.6 Assessment of Event Expectedness

If the event could possibly, probably or definitely be related to trial treatment, an initial assessment of the expectedness of the event should be made by the investigator. The medical officer based at the STOP-HCV-1 Co-ordinating Centre will then also assess the expectedness of the event. Following their review of the event, the medical officer may have questions or ask for more information relating to the event; these will be sent to the site trial team via email.

The STOP-HCV-1 Co-ordinating Centre will issue a file note listing the current trial approved Summary of Product Characteristics (SmPCs) and send sites an updated file note each time these are changed throughout the trial. The SmPCs listed on the file note should be used by the investigator to perform their assessment of relatedness and expectedness. The investigator should also note which Ribavirin brand the participant was dispensed and therefore confirm which SmPC their assessment was performed against. This will allow the medical officer at the STOP-HCV-1 Co-ordinating Centre to assess the relatedness of the event to the correct brand of Ribavrin.

An unexpected adverse reaction is one not previously reported in the current trial approved SmPCs or one that is more frequent or more severe than previously reported. The definition of an unexpected adverse reaction (UAR) is given in table 8. If a SAR is assessed as being unexpected, it becomes a SUSAR.

21.3 Notification Process

- **Form 10a – Serious Adverse Event** must be completed by an investigator named on the Signature and Delegation of Responsibilities Log, who is responsible for the patient's care. Particular attention must be paid to the grading, causality and expectedness of the event as outlined above. In the absence of the responsible investigator, the form should be completed and signed by another member of the site trial team.
- The responsible investigator should subsequently check the SAE Form, make changes as appropriate, sign and then re-send to the STOP-HCV-1 Co-ordinating Centre as soon as possible. The initial report must be followed by detailed, written reports as appropriate.
- **Typed narrative** - In addition to **Form 10a – Serious Adverse Event,** a typed narrative summarising the event should be submitted. It should include the clinical presentation and progression of the event, any treatments given in response to the event, any relevant tests carried out and any likely causes of the event other than the study medication the participant is taking. It should also include a rationale for the investigator's assessment of causality and expectedness to the STOP-HCV-1 study medication. A narrative template is available, if required, please make a request via email to the STOP-HCV-1 team at mrcctu.stophcv1@ucl.ac.uk.
- The minimum criteria required for reporting an SAE are the participant trial number, initials, date of onset, event number on this date, the SAE name, and an indication of why the event is considered serious. The SAE form must be signed by an appropriate person as specified above. The SAE Form must be sent to the STOP-HCV-1 Co-ordinating Centre by secure email mrcctu.stophcv1@ucl.ac.uk or by fax to **0207-670-4817.**
- The Date of Onset recorded on Form 10a - Serious Adverse Event should be the date that the event met the serious event criteria, not the date the work-up started. For example, if the participant developed symptoms prior to being admitted to hospital, but these symptoms did not meet the reporting criteria; the date of onset should be recorded as the date of hospital admission rather than the date the symptoms developed.
- The Date of Resolution recorded on Form 10a - Serious Adverse Event should be the date that the event stopped meeting the serious event criteria. For example, for an event that was reported due to a hospital admission, the date of discharge should be recorded as the date of resolution. If the participant's condition has not fully resolved, then the investigator may choose to update the Event Status as "Resolved with sequelae".
- On Form 10a, all trial medication (both first line and retreatment) the participant has been prescribed through the duration of the trial should be documented in Section C, Trial Medication.

- On receipt of a SAE form, the STOP-HCV-1 Co-ordinating Centre will acknowledge receipt of the event via email. If you do not receive this acknowledgement within 24 hours of sending the event, you should assume that the event has not been received. Please re-send and/or contact a member of the trial team at the STOP-HCV-1 Co-ordinating Centre if email confirmation has not been received in the required time.
- Staff should follow their institution's procedure for local notification requirements.

21.4 Non-Serious Adverse Event

All non-serious adverse events and reactions should be recorded in the patient's medical records; only those which meet the following criteria are required to be reported on the **Form 11 - Non-Serious Adverse Event** whether expected or not and within **7 days of site awareness** .

- Grade 3 or 4 adverse events or reactions
- An event that leads to the modification of one or more trial drugs (any grade)
- Grade 3 or 4 laboratory abnormalities in the absence of clinical symptoms.

If an adverse event is both serious (following the table above) and grade 3 or 4, only report it once on **Form 10a – Serious Adverse Event.**

21.5 Follow-up of Events

Patients must be followed up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised.

Follow-up should continue after completion of protocol treatment if necessary. As information regarding the event becomes available the SAE form and narrative should be updated with the new information, ensuring that any corrections have been appropriately indicated as per the CRF completion guidelines above and sent to the STOP-HCV-1 Co-ordinating Centre. Extra, annotated information and/or copies of test results may be provided separately. The patient must be identified by trial number and initials only. **The patient's name should not be used on any correspondence and should be deleted from any test results.**

21.6 Management of Pregnancy

The oral DAAs are pregnancy category B drugs based on data in the pre-clinical setting. Very few women have actually had exposure to any of the modern DAAs during pregnancy.

Ribavirin (RBV) is a Category X drug in pregnancy.

In the first part of the study, there is 1 in 2 chance of being randomised to receive adjunctive RBV. In the retreatment phase all patients who require retreatment on the study will receive 12 weeks of RBV.

The protocol is written to exclude those who are currently pregnant, or intending to become pregnant (self or partner) during the study. Because of the potential prolonged effects of

RBV on pregnancy or spermatogenesis post-exposure, the protocol recommends avoidance of pregnancy in females of CBP for at least 4 months after last exposure to RBV and for males with a female partner, avoidance of pregnancy for at least 7 months after last exposure to RBV.

Women of CBP have pregnancy testing throughout the study. Heterosexual men are reminded at each study visit of the importance of avoiding pregnancy in their female partners for the durations as detailed above.

21.6.1 Female participant on study becomes pregnant – direct DAA +/- RBV exposure

Should a female trial participant become pregnant before completion of study follow-up, they should be recalled for confirmatory testing as soon as practicable. The pregnancy and its outcome must be reported as an SAE. If pregnancy is confirmed the participant should be counselled on the risks. The risks will depend on the following:

1. actual direct exposure to DAA +/- RBV during pregnancy vs.
2. no exposure to DAA +/- RBV during the pregnancy, but possible 'tail' effects of RBV because pregnancy occurred in the 4 months window after last dose of RBV.

The clinician should source the latest data available on direct exposure from the Ribavirin Pregnancy Register (sources include Roberts et al 2010, www.ribavirinpregnancyregistry.com).

If the patient is on treatment at the time they have confirmed pregnancy, and given the unknown risks of DAA in 1st trimester it is likely that participants will be advised to stop treatment even if not receiving Ribavirin.

However, given the risk of transmission to infant in HCV positive women, this decision will rest with the participant and their clinician. Whatever the decision re the DAA (continue vs. stop), RBV must be stopped immediately, this is especially important if the women opts to **continue** the pregnancy.

Should the participant wish to consider termination they will be referred to local services for discussion in consultation with the study team.

Information on pregnancy outcome in women directly exposed to RBV will be reported to the MHRA and to the Ribavirin register.

21.6.2 Female partner of participant becomes pregnant during or within 7 months of RBV exposure – indirect exposure

Pregnancies in female partners of a male trial participant, either during his treatment or within 7 months of last dose of RBV, will be reported as an SAE.

A separate consent has been developed to seek specific information from indirectly-exposed female partners to obtain information on the pregnancy and its outcome. The participant and his partner (with her permission) should be counselled on the risks to the foetus based on

the latest data available on indirect exposure from the Ribavirin Pregnancy Register (e.g. Roberts et al 2010). Should the trial participant's partner wish to consider termination they will be referred to local services for discussion in consultation with the study team.

This information on pregnancy outcome will be reported to the MHRA and to the Ribavirin register.

22 Monitoring and Quality Management

22.1 Investigator Site File Maintenance

Sites will be provided with an Investigator Site File (ISF). This file should be maintained and kept up to date until trial closure. Prior to site opening sites will be required to complete and sign an Initial Investigator Site File Self-Assessment Form, which will confirm that all necessary documents are filed. During the trial, following approval and implementation of a substantial amendment or if any important documents are sent to site, sites will be sent copies of the documents along with a confirmation of receipt document.. This should be signed and returned to the STOP-HCV-1 Co-ordinating Centre confirming that all the new documents have been reviewed and filed in the ISF. The original confirmation of receipt should also be filed in the ISF.

22.1.1 CVs and GCP certificates

The STOP-HCV-1 Co-ordinating Centre will only ask for copies of the Principle Investigator's and Drug Manager's CV and GCP certificate to be sent to them; however it is expected that CVs and GCP certificates for all sub-investigators and research nurses are kept on file at site. CV's should be signed and dated within the last 2 years and GCP certificates should be dated within the last 3 years. A review of these documents should be conducted at least annually to ensure that all are in date throughout the course of the trial.

22.2 Quality Management and Control

Sites are responsible for implementing and following their own local quality management procedures. This should ensure that all trial documents are maintained (for example the Site Signature and Delegation Log) and data reported is accurate. Sites should consider having a team member check and verify CRFs after completion to ensure that the data recorded matches that in the source documentation.

22.3 On-site monitoring visits

Members of the STOP-HCV-1 co-ordinating team will aim to conduct an on-site monitoring visit within the first year after recruitment of the site's first participant. Prior to the monitoring visit sites will receive a pre-visit monitoring letter outlining the monitors plan for the visit. During the visit the monitors will visit the main clinic to review patient notes and the ISF, pharmacy to review the pharmacy files and confirm the participant was dispensed drug corresponding to their drug allocation, and the laboratory to check the sample management. Following the visit a report and action item summary will be sent to site, outlining any findings and actions to be followed up after the visit.

23 Appendix

23.1 Appendix 1: STOP-HCV-1 Treatment Failure Guidance

Criteria (i)

To meet criteria (i) the participant must have had:

- Two HCV VL below the lower limit of quantification (LLOQ) in a row at any time up until Post First-line EOT+24
- Followed by one HCV VL above the LLOQ
- Confirmed by one HCV VL above 2000 IU/ml **at least** one week (i.e. ≥7 days) after the first HCV VL above the LLOQ

Example:

Visit	HCV VL IU/ml	Absolute result/ Assay lower limit
Enrolment	200000	Absolute result
Day 03	80	Absolute result
Day 07	<15	Assay lower limit
Day 14	<15	Assay lower limit
First line EOT	<15	Assay lower limit
Post First line EOT+4	1700	Absolute result
Unscheduled (7 days following Post FL EOT+4)	50000	Absolute result

Criteria (ii)

To meet criteria (ii) the participant must have had:

- One HCV VL above 2000 IU/ml which is also more than 1 $\log_{10}$ increase (10 times higher) than the patient's lowest HCV VL on trial treatment (includes the assay lower limit value).
- Confirmed by a second HCV VL above 2000 IU/ml and more than 1 $\log_{10}$ increase from the lowest HCV VL on trial treatment **at least** one week (i.e. ≥7 days) after the first.

Example:

Visit	HCV VL IU/ml	Absolute result/ Assay lower limit
Enrolment	200000	Absolute result
Day 03	80	Absolute result
Day 07	40	Absolute result
Day 14	20	Absolute result
First line EOT	<15	Assay lower limit
Post First line EOT+4	1700	Absolute result
Post First line EOT+8	30000	Absolute result
Unscheduled (7 days following Post FL EOT+8)	50000	Absolute result

What to do if a participant returns and has:

A detectable HCV VL following two consecutive HCV VL results below the LLOQ.

- The participant could potentially meet criteria (i). The participant should be recalled for a second HCV VL **at least one week after** the first detectable HCV VL for the confirmatory HCV VL to be taken.

A detectable HCV VL above 2000 IU/ml and a 1 $\log_{10}$ increase from the lowest value on treatment and the participant has never had two consecutive HCV VL results below the LLOQ.

- The participant could potentially meet criteria (ii). The participant should be recalled for a second HCV VL **at least one week after** the first HCV VL above 2000 IU/ml for the confirmatory HCV VL to be taken.

A detectable HCV VL **below** 2000 IU/ml and 1 $\log_{10}$ increase from the lowest value on treatment and the participant has never had two consecutive HCV VL results below the LLOQ.

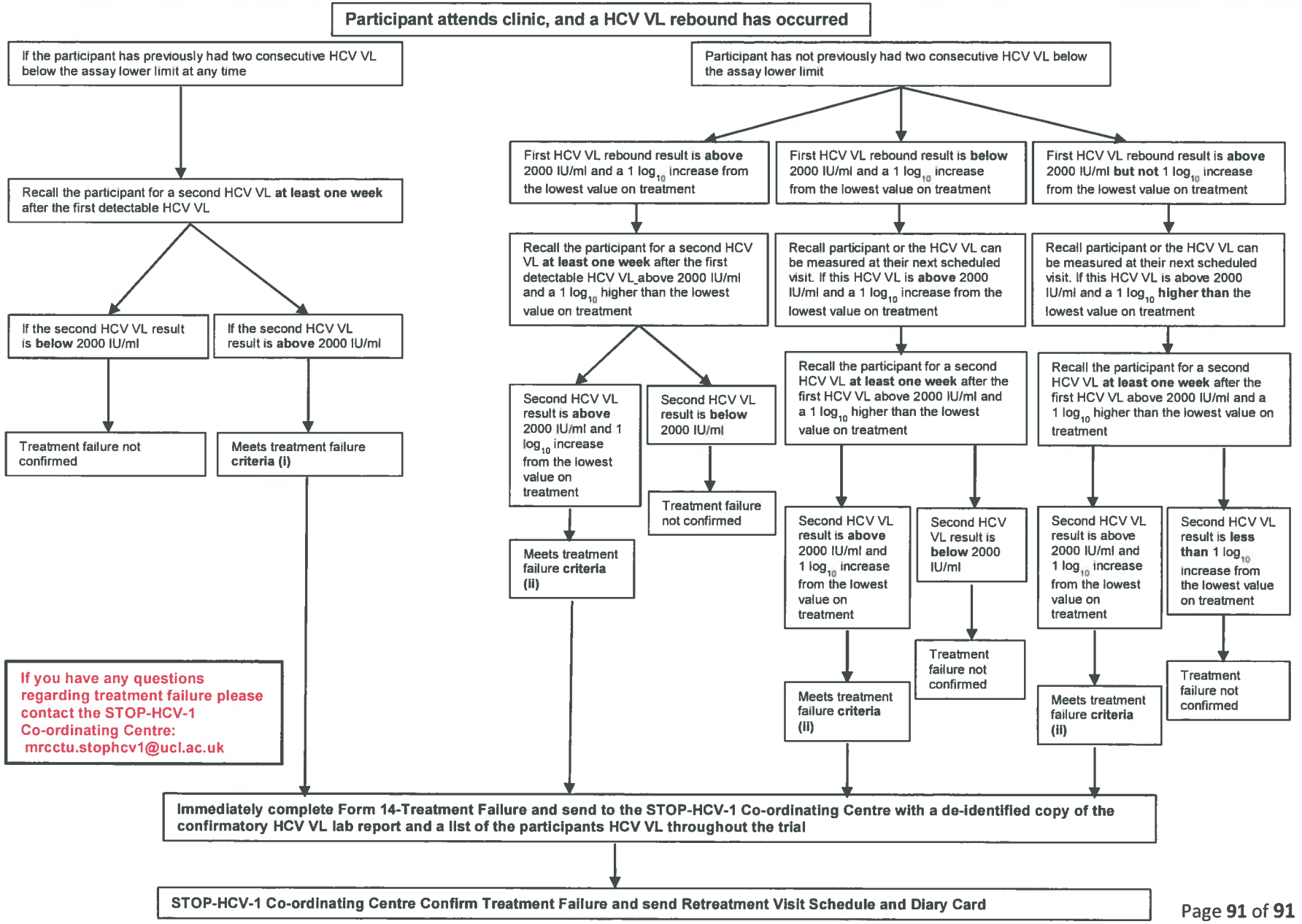
- The participant can either be recalled for another HCV VL or HCV VL can be measured at their next scheduled visit – the decision to request the participant to return is at the treating physician's discretion. If the next HCV VL is then above 2000 IU/ml and 1 $\log_{10}$ higher than the lowest value on treatment, the participant could potentially meet treatment failure criteria (ii) but this result is not considered the confirmatory result, because it is the first one to actually potentially meet the failure criteria. The participant should then be recalled for a second HCV VL **at least one week after** the first HCV VL above 2000 IU/ml and 1 $\log_{10}$ higher than the lowest value on treatment for the confirmatory HCV VL to be taken.

A detectable HCV VL above 2000 IU/ml **but not a** 1 $\log_{10}$ increase from the lowest value on treatment.

- The participant can either be recalled for another HCV VL or HCV VL can be measured at their next scheduled visit – the decision to request the participant to return is at the treating physician's discretion. If the next HCV VL is then above 2000 IU/ml and 1 $\log_{10}$ higher than the lowest value on treatment, the participant could potentially meet treatment failure criteria (ii) but this result is not considered the confirmatory result, because it is the first one to actually potentially meet the failure criteria. The participant should then be recalled for a second HCV VL **at least one week after** the first HCV VL above 2000 IU/ml and 1 $\log_{10}$ higher than the lowest value on treatment for the confirmatory HCV VL to be taken.

If in any of the scenarios the confirmatory HCV VL result is **below** 2000 IU/ml, the process of identifying a treatment failure starts again, as required following the potential criteria the participant would meet listed on page 1.

See section 11, for the procedure of reporting a treatment failure following receiving a confirmatory HCV VL which meets the criteria.


Participant attends clinic, and a HCV VL rebound has occurred
If the participant has previously had two consecutive HCV VL below the assay lower limit at any time
Recall the participant for a second HCV VL at least one week after the first detectable HCV VL
If the second HCV VL result is below 2000 IU/ml
If the second HCV VL result is above 2000 IU/ml
Treatment failure not confirmed
Meets treatment failure criteria (i)
Participant has not previously had two consecutive HCV VL below the assay lower limit
First HCV VL rebound result is above 2000 IU/ml and a 1 log10 increase from the lowest value on treatment
First HCV VL rebound result is below 2000 IU/ml and a 1 log10 increase from the lowest value on treatment
First HCV VL rebound result is above 2000 IU/ml but not 1 log10 increase from the lowest value on treatment
Recall the participant for a second HCV VL at least one week after the first detectable HCV VL above 2000 IU/ml and a 1 log10 higher than the lowest value on treatment
Recall participant or the HCV VL can be measured at their next scheduled visit. If this HCV VL is above 2000 IU/ml and a 1 log10 increase from the lowest value on treatment
Recall participant or the HCV VL can be measured at their next scheduled visit. If this HCV VL is above 2000 IU/ml and a 1 log10 higher than the lowest value on treatment
Second HCV VL result is above 2000 IU/ml and 1 log10 increase from the lowest value on treatment
Second HCV VL result is below 2000 IU/ml
Treatment failure not confirmed
Meets treatment failure criteria (ii)
Recall the participant for a second HCV VL at least one week after the first HCV VL above 2000 IU/ml and a 1 log10 higher than the lowest value on treatment
Recall the participant for a second HCV VL at least one week after the first HCV VL above 2000 IU/ml and a 1 log10 higher than the lowest value on treatment
Second HCV VL result is above 2000 IU/ml and 1 log10 increase from the lowest value on treatment
Second HCV VL result is below 2000 IU/ml
Treatment failure not confirmed
Meets treatment failure criteria (ii)
Second HCV VL result is above 2000 IU/ml and 1 log10 increase from the lowest value on treatment
Second HCV VL result is less than 1 log10 increase from the lowest value on treatment
Treatment failure not confirmed
Meets treatment failure criteria (ii)
If you have any questions regarding treatment failure please contact the STOP-HCV-1 Co-ordinating Centre: mrcctu.stophcv1@ucl.ac.uk
Immediately complete Form 14-Treatment Failure and send to the STOP-HCV-1 Co-ordinating Centre with a de-identified copy of the confirmatory HCV VL lab report and a list of the participants HCV VL throughout the trial
STOP-HCV-1 Co-ordinating Centre Confirm Treatment Failure and send Retreatment Visit Schedule and Diary Card