Viral Hepatitis Clinical Research Program

Manual of Operations

Instructions for study procedures for VHCRP studies

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For all protocol, study or site management related questions, please contact the study specific Project Coordinator.

This manual is complementary to the protocol and is intended to provide a comprehensive resource to help investigational sites with the conduct of VHCRP studies.

The manual contains general guidelines on study procedures such as handling of clinical supplies and managing study documentation.

Study specific contacts, procedures and guidelines are provided in a study specific supplement.

At any time, if you have difficulty with a procedure contact the study specific Project Coordinator for assistance.

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1. Communication and Contacts

***Refer to the study specific contacts for details of your Kirby Institute study contacts*.**

In most cases, communication with investigators and staff regarding the study will take place via electronic mail. E-mail will be used to distribute participant management reports, data queries and other materials as well as for routine contact with the sites. This will allow rapid and uniform communication across time zones and ensure that all participating investigators stay informed about the conduct and progress of the study.

2. Study Visits

1.1 Screening and Enrolment/Baseline Visits

Prior to performing any study assessments the patient must consent to the study.

For studies that have a screening visit the screening log for this study is electronic and combined with the electronic enrolment log as part of the 'Enrolment Tracker'. It is an electronic Excel Spreadsheet named 'Site Enrolment Tracker' and consists of two worksheets:

1. Enrolment Tracker
2. Projected Visits (as applicable)

Each site will be provided with this spreadsheet. Please update and send this spreadsheet by email to the Project Coordinator when a participant is **screened** and if eligible, when they are **enrolled** and allocated their study Participant ID.

Only enter data into the *Enrolment Tracker worksheet*, the *Projected Visits worksheet* will be automatically populated once you have entered data into the Enrolment Tracker.

1.1.1 Enrolment Tracker worksheet

Once a participant has signed the Participant Consent Form, enter the details of the participant into the Enrolment Tracker. To be eligible to participate in the study, a participant must satisfy all of the eligibility criteria listed in the protocol. *Only study participants who have consented to participate in the study should be entered into the Enrolment Tracker.*

1.1.2 The Participant Identifier

Each participant will be identified by a study number (participant unique study ID) and the participant's initials.

1.1.3 At Screening

For most studies, upon screening allocate the participant a screening ID number. The screening ID numbers are in your electronic Enrolment Tracker. The screening ID number allocated must match the number on the screening lab kit selected.

Screening ID: XXX-001 e.g. 333-040

⇒ update the Enrolment Tracker and send to the Project Coordinator

If the participant is baselined (enrolled onto the study), then allocate the participant the next available Study Participant ID.

Study Participant ID: YYYY-ZZZZZ-01 or YYY-ZZZZZ-001 where YYYY is the protocol number and ZZZZZ is the site number e.g. 1510-61201-15

⇒ update the Enrolment Tracker and email to the Project Coordinator

The available Participant ID numbers are pre-populated in the Enrolment Tracker worksheet. The participant ID numbers are locked and cannot be changed. Please contact the Project Coordinator if you have any questions about allocating ID numbers to participants.

A participant's initials are made up of four letters: the first two letters of the participant's **last name** followed by the first two letters of the participant's **first name**.

For example, Smith John, initials is SM-JO.

The following information, where applicable, should be entered into each column specified below in the Enrolment Tracker for consented participants (example in Figure 1). Note: the number, name and order of columns may vary based on the study design:

- Study Screening ID e.g. 444-013
- Screening date
- 2x2 initials - Last name, First Name (for example, enter SM-JO for John Smith)
- Participant Date of Birth (DOB) - dd/mm/yyyy
- Consent for sub-study – select 'Yes' or 'No' from the drop-down menu (if applicable)

1.1.4 Enrolment

Continue to enter data in this worksheet if a participant is eligible and enrolled into the study. Enter the baseline date once the participant is confirmed as eligible and enrolled into the study. The baseline date must be after the screening date.

Enter the rest of the enrolment data in the white columns of the worksheet. Once you have entered data into this worksheet, the 'Projected Visits worksheet' will be automatically populated.

The following information, where applicable, should be entered into each column specified below in the Enrolment Tracker for consented participants

- Column E: Eligible – select 'Yes' from the drop-down menu
- Column I: Enrolment – if the Participant is enrolled, select 'Yes' from the drop-down menu
- Column J: Baseline Date – dd/mm/yyyy
- Coulmn K: Subject ID e.g. 1510-61201-04

DARLO-C Screening ID	Screening date	Secondary ID Patient 2x2 name code (Surname/First name)	Patient DOB	Eligible (yes/no)	Reason(s) for exclusion	Specify exclusion reason	Consent for sub-study (yes/no)	Enrolment (yes/no)	Baseline Date	DARLO-C Subject ID	Withdrawn/Lost to follow up Date	Early Treatment Stop date	Complete
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			
XXX-XXX										1510-XXXXX-XX			

Figure 1: Example of an Enrolment Tracker

1.2 Screening failures

If a participant consents but is found to be ineligible to participate in the study, the following data should be entered (Figure 2):

- Column E: Eligible – select 'No' from the drop-down menu
- Column F: Reason for exclusion – select the reason from the drop-down menu optionsColumn G: Specify other – if 'Other' is selected in Column F
- Column I: Enrolment – if the participant is ineligible, select 'No' from the drop-down menu
-

Eligible (yes/no)	Reason(s) for exclusion	Specify exclusion reason	Enrolment (yes/no)

Figure 2: Excluded Participant - Enrolment Tracker Completion

No further data entry is required for participants who are ineligible and are not enrolled in the study.

1.3 Rescreening

If a participant does not meet the eligibility criteria, the protocol may allow the participant to be enrolled at a later point in the study if eligibility criteria are then met. The participant will be allocated a different Screening ID (XXX-XYZ e.g. 444-425) and the Enrolment Tracker should be updated with the new screening date.

⇒ use a different Screening ID with the new SCR date

The updated Tracker is to be emailed to Project Coordinator when participant is screened /rescreened and also when enrolled.

1.4 Protocol Exemption Procedure

1.4.1 Exemption for eligibility criteria

Only eligible participants should be enrolled into the study. However, on some occasions, a protocol exemption may be required to allow a study participant to enroll in the study. Any deviations from the eligibility criteria will require a protocol exemption from the designated project personnel. A protocol exemption form is to be completed by the site investigator/study coordinator and e-mailed or faxed to the Study Project Coordinator. If the protocol exemption is granted, a protocol exemption number will be allocated on the form and faxed/emailed back to the site. The site can go ahead and enroll the participant.

The protocol exemption number will be required to be entered into the screening section of the electronic CRF. There is a question in the eligibility criteria section which asks whether a protocol exemption is granted and the number of the exemption. The protocol exemption number received from the Study Project Coordinator on the protocol exemption form should be entered here.

Refer to your study specific supplement for the study specific Protocol Exemption Form.

1.4.2 Exemption during the study

The study should be conducted in compliance with the study protocol at all times. Investigators should not implement any deviations from the protocol unless agreed by the Kirby Institute or where necessary to eliminate an immediate hazard(s) to a study participant. The same protocol exemption procedure for eligibility criteria will be followed by the site investigator or study coordinator to obtain a protocol exemption during the study. The Study Project Coordinator will e-mail or fax back the protocol exemption form with the protocol exemption number. However, this protocol exemption number will not be entered into the e-CRF. All protocol exemptions will be submitted to the Lead Ethics Committee in the annual report and tracked in a tracking database at the Kirby Institute. Protocol exemptions should be reported to the local Human Research Ethics Committee in accordance with local requirements. All protocol exemption forms must be kept at sites and filed in the Investigator Site Folder.

Refer to your study specific supplement for the study specific Protocol Exemption Form.

1.5 The Master Participant Enrolment Log

It is an ICH GCP requirement that each site keeps a confidential list of names and details of all participants allocated trial numbers on enrolment to the trial. This allows the site to identify any study participant if required.

Sites will be provided with a blank hard-copy Master Participant Enrolment Log which records details including Participant Study ID Number, Participant Name, Medical Record Number/Participant ID Number, Date of Birth, Emergency Contact Details, Study Enrolment Date and Completion Date. Completion of this list should be the first step taken when a participant is entered in the enrolment tracker.

This list must be kept up to date. It should be available for inspection by Kirby Institute personnel, including monitors and auditors, but will under most circumstances be copied or collected by Kirby Institute personnel. If the list is required to be copied or collected then approval must be sought by The Kirby Institute.

Refer to your study specific supplement for the study specific Master Participant Enrolment Log.

1.6 Study Visits and required Procedures

Refer to the study specific protocol and study specific supplement for details of the assessments required for each study visit.

All assessments outlined in the schedule of assessments should be performed at each study visit. If a study visit is not going to be attended or a specific assessment is not going to be performed you must apply for a protocol exemption otherwise it will be noted as a protocol deviation.

Continue to enter data in the enrolment tracker worksheet as the participant progresses through the study. Enter the following information as it occurs.

- Withdrawn/Lost to follow-up Date – dd/mm/yyyy
- Early treatment Stop Date – dd/mm/yyyy
- Complete – select 'Yes' or 'No' from the drop-down menu

For most study protocols at each clinic visit, if any of the following have occurred since the last visit, they will need to be reported as indicated:

Refer to the study specific protocol for study specific requirements.

- **Adverse events**: record on the adverse events (AE) eCRF;
- **Serious adverse events (SAEs)**: record on the AE eCRF and on the SAE form. Submit the appropriate form and supporting documentation by fax or email to the Study Project Coordinator on +61 2 9385 9214. SAEs may also be required to be submitted to the pharmaceutical company funder. Check the study protocol for details.
- **Changes to concomitant medications**: record on the concomitant medication (CM) eCRF.
- **Recurrent adverse events**: in case an adverse event is recurrent throughout the study (e.g. headaches, on and off during the study), report the adverse event on a single eCRF form. Document the start date of the event, and do not enter any stop date until the event is completely resolved. Once resolved, enter the highest grade the participant has experienced

Please remember to follow-up adverse events at subsequent visits to ensure that events are resolved.

Projected Visits worksheet (if applicable)

This worksheet contains the projected visits for the participants.The projected dates are auto-populated from the dates entered on the enrolment tracker worksheet.

The following dates and answers in the enrolment tracker worksheet are used to calculate the projected visits:

- ***Baseline Date*** – all visit dates are calculated from the baseline date.
- ***Withdrawn and Lost To Follow Up (LTFU) date*** – if a participant has been lost to follow up (FU) or withdrawn from the study, enter the date into the column and all projected visits will disappear as you will no longer follow up the participant in the study.
- ***Early treatment stop date*** – if a participant stops treatment earlier than the prescribed duration for any reasons, enter the stop date in this column. Subsequent projected visit dates (as applicable) will calculate from the early treatment stop date, and any previous projected dates before the early treatment stop date is entered, will disappear. The early treatment stop date =end of treatment response (ETR) visit date.

1.7 Early termination, withdrawal, lost to follow-up and patient movements

1.7.1 Participants who move

It is expected that during the follow-up period of a study, some participants will move away from the area where they are being seen for the study. If a participant moves to a place where there is another study site where they can be followed, the participant may be transferred to that site. Please advise the Study Project Coordinator and they will assist you in arranging for a participant to be transferred to another participating site. The Project Team will organise to provide the new site with access to the participant's eCRF. Your responsibilities are to provide a copy of the participant's medical record, including a copy of the signed Participant Informed Consent form and help to arrange the first visit at the new site. It is your responsibility to ensure that all eCRF data queries are closed out prior to the participant transferring to the new site. The new site will need to re-consent the participant and notify the Project Coordinator that the transfer has been completed.

Once the participant has been successfully transferred, the participant record on the eCRF will be moved to the new site. Even though the participant is transferred to a new site, the Participant Identification number will remain the same.

Follow-up of the participant will remain your site's responsibility until the participant signs a Participant Informed Consent form at another participating site.

If a participant moves to a place where no other participating site is available, the Project Team may be able to help you make arrangements with the participant and his or her new physician to continue collecting study data for the duration of the study with the written consent of the participant if feasible. Data may be collected by phone contact, email, fax or by letter from the participant or the participant's physician. You should document such contacts in the participant's file at your site, and report on each study eCRF all of the data that are available to you.

1.7.2 Involuntary incarceration or imprisonment

If a participant becomes a prisoner or is involuntarily incarcerated during the course of a study, all research interactions and interventions should cease until the participant is released from the facility or institution. This includes obtaining any identifiable private information about the now incarcerated participant.

In circumstances where the Principal Investigator believes that it is in the best interests of the participant to remain in the study while incarcerated, then the participant may continue to have access to the study drugs and safety checks, provided local authorities allow this to occur.

Please notify the Project Coordinator immediately if you become aware that a participant has been incarcerated.

1.7.3 Withdrawal of Consent

A participant has the right to withdraw consent to participate in any aspect of the protocol. For example, at any visit, a participant may refuse to take study treatment or to have blood drawn, may refuse to (or be unable to) attend scheduled protocol follow-up visits or may choose to move to another city. None of these imply refusal to have any data collected, or for data already collected to be included in analyses. In almost all cases, some data can continue to be collected (e.g. through clinic visits, medical records abstraction, phone contact with the participant or the participant's contact persons or physician). Unless a participant states otherwise, it should always be assumed that the participant consents to have at least vital status

reported. However, if a participant refuses to have any data reported, and if after site staff have discussed with the participant different options for reporting even minimal data (e.g. vital status) the participant still refuses to allow any data to be reported, you need to respect and report this withdrawal of consent. It is recommended that this decision is made in consultation with the Site Principal Investigator.

When a participant explicitly withdraws consent to have any data reported:

- document all communication surrounding the participant's withdrawal of consent in the participant's file and if possible, every effort should be made to have the participant sign the revocation of consent section in their consent form (if applicable)
- contact the Study Project Coordinator and provide them with the Participant Identification number, initials, date of birth, site number and the date that the participant withdrew consent
- complete the Study Completion (SC) page in the eCRF for the participant
- do not collect any data after the consent withdrawal date
- do not complete any further eCRF pages for the participant.

At any time, participants can change their mind about withdrawal of consent and resume participation in a study. If this happens, please notify the Project Coordinator and inform them that the participant is resuming follow-up at a particular date. Do not complete follow-up visits from the period when the participant had withdrawn consent. Should the participant choose to re-consent, please have the participant sign another consent form and resume follow-up visits on the participant's Data Collection Schedule from the date of re-consent.

1.7.4 Lost to Follow-up

Please make every effort to keep study participants in follow-up. Please collect adequate contact details to allow potential participants to be followed up. Only recruit those participants who you think will remain in the study for the whole study duration. Even if there has been no contact with the participant for more than 6 months, please keep trying to contact the participant and to collect data at each scheduled visit. Only mark the participant as Lost to Follow-up once instructed by the Data Manager.

3. Study Drugs (if applicable)

1.8 Study Drug Supply, Storage and Dispensing

Refer to the study specific protocol for details of the study drug supply, storage and dispensing (if applicable).

1.9 Study Drug Prescribing

It is the responsibility of the Investigator to ensure that study products are only dispensed to study participants and by suitably trained, authorised personnel according to local regulations at recognised hospital and clinic pharmacies. The drug will be dispensed by the clinic pharmacist to the study investigator or a qualified member of the investigational staff or directly to the study participant as specified in the study specific supplement.

All prescriptions (or equivalent documentation) must be signed by a clinician who satisfies the requirements for being an 'authorised prescriber' and who is delegated to perform this task by the Site Principal Investigator on the Site Signature and Responsibility Log. By signing the prescription, the clinician

is taking full responsibility for ensuring that the prescription conforms to the protocol and to all applicable laws and regulations. It is recommended that prescriptions are double-checked by the Study Coordinator. Prescriptions may be hand-written with ink, typed or generated by computer.

1.10 Study Drug Dose and Schedule

Refer to the study specific protocol for details of the study drug dose and schedule.

1.11 Study Drug Accountability and Destruction

For studies where clinical trial drug is used details of drug accountability and destruction procedures will be provided to the pharmacy in a pharmacy manual.

4. Clinical Assessments and Management

The study protocol will detail which clinical assessments are required at each study visit, how to manage toxicities and prohibited or contraindicated medications. The Investigator Brochure or Product Information will provide details on the safety profile of the study medication.

1.12 Medical History

To be conducted at Screening by recording all clinically significant illness currently as per the study protocol.

1.13 Physical Measurements

Refer to the study specific protocol for details of the physical measurements to be conducted at each study visit.

1.14 Laboratory Assessments

Refer to the study specific protocol for details of the study laboratory assessments required for each study visit.

1.15 Toxicity management

Clinical symptoms of any drug toxicities are generally required to be documented on the adverse event form. For detailed instructions on adverse event reporting, please refer to the study protocol. If concomitant medications are required to manage the symptoms of adverse events, these generally should be recorded on the concomitant medication eCRF.

Refer to the study specific protocol for detailed instructions on adverse event reporting.

1.16 Prohibited medications

The prescribing information for all concomitant drugs should be consulted and reviewed carefully. The determinations listed in the respective contraindicated, warning, and precaution sections must be respected in order to prevent any potentially serious and/or life-threatening drug interactions.

In case of any questions on potential interactions with a drug, please contact the Study Principal Investigator.

Refer to the study specific protocol for details of the prohibited medications and required washout periods.

If at any time you are unsure about drug-drug interactions contact the Study Principal Investigator immediately for advice.

5. Data Collection

An electronic data capture (EDC) system, OpenClinica, will be used for **VHCRP studies** and will require sites to enter the majority of the data onto an electronic case record form (eCRF). This system enables many data queries to be automatically generated and resolved, eliminating the need for human intervention and therefore reducing the life cycle of data queries. There are many checking mechanisms built into the eCRF system, designed to reduce transcription errors and improve the quality of the data collected, thereby minimising the time for data analysis. There are also instructions in the "OpenClinica Site User Manual".

Training in the EDC will be provided by the Project Coordinator or Data Manager as part of the Study Initiation Meeting. In the event of new site personnel, new versions of the EDC system, protocol or Participant Information and Consent Form amendments, further training in the EDC system might be required.

The study nurse may also request additional training in the EDC system at any time.

1.17 Overview

Screening visit:

There are no screening failures entered into the eCRF system. They are however collected on the 'Enrolment Tracker', which is described in section 2.1 The screening visit eCRF should be completed only when a participant is baselined i.e. enrolled onto the study.

Baseline visit:

The baseline visit eCRF should be completed only when a participant is eligible to be enrolled onto the study.

On-treatment visits or follow-up visits:

All subsequent study visits will be displayed in the eCRF.

End of Treatment (ETR) visit:

The ETR visit is completed when a participant has either finished their study medication or stopped treatment prior to completion of treatment for any reason.

1.18 Principles of data collection

The eCRF should always be as accurate and up-to-date as possible.

Several elements contribute to achieving this goal:

- Training of Study Personnel
- Initiation meetings will be held prior to the commencement of the study. All coordinators and investigators must attend an initiation meeting. The protocol, eligibility criteria, laboratory and pharmacy specifics, the eCRF, randomisation procedures and serious event reporting will be discussed at this meeting
- Quality management activities
- Ongoing site training and feedback from the Project Team.

1.19 Source Documentation

All data required on the eCRF must be verifiable in the participant's medical record, including:

- specific eligibility criteria
- lab measurements
- clinical measurements (e.g. height and blood pressure)
- information obtained by participant self-report
- any participant contact through which data are collected
- any medications prescribed
- any adverse clinical events
- serious adverse events.

Source documentation requirements are outlined in Section 7.6 of this Manual. Source document templates are available from the Project Team. All participant record entries must be signed and dated by the clinician who saw the participant.

1.20 Timely and Accurate Electronic Case Report Form (eCRF) Completion

eCRFs should be completed by individuals who have received training at the start of the study and who are familiar with the study visit and data collection requirements. Do not share usernames and passwords.

eCRFs should be completed as soon as possible after the participant visit (please enter the date of visit as a minimum, and as much information as possible regarding that visit).

Laboratory results should be entered into the eCRF as soon as available.

Incomplete forms that do not have adequate explanation compromise the integrity of the entire study. Errors, such as incomplete or illegible forms, are problems that require time and energy to resolve.

1.21 Data Queries

Some data queries will be automatically generated immediately when data are entered into the EDC. Automatically generated data queries are created when data are entered and fall outside a predefined range. For example, scheduled visit windows and laboratory normal ranges.

On review of entered data, a Project Team member may also raise data queries electronically on the eCRF. Data query reports will be sent by email from the Project Team. Sites will work with the Project Team to resolve these queries and ensure that the correct information is received in a timely manner.

Please see the OpenClinica Site User Manual for instructions on how to change data and resolve data queries on the eCRF.

Following data review, data queries will be generated by the Project Team within 2 weeks of receipt of eCRFs.

- The ultimate responsibility for responding to data queries lies with the Principal Investigator.
- The site should respond to data queries within 2 weeks of receiving them.
- All data corrections should be made directly on the eCRF. This method assures that all changes to the eCRF can be easily observed when the participant's records are monitored or audited.
- The Project Team may work with the site clinician or coordinator to correct errors (e.g. via phone or e-mail), as long as the eCRF at the site accurately reflects the changes made.
- If changes to data are made, then a relevant data query or reason must exist on the eCRF.

Depending on the project, further confirmation of data may occur outside of OpenClinica. The study Data Manager will provide more information to the Site if required.

1.22 Dates

All dates will be recorded in the day/month/year format, i.e. 10 October 2009 should be recorded as "10/Oct/2009". If the actual day is unknown please complete as the 15th of the month, if the month is unknown, please complete as June. If the day and month are not known, '15th June' should be used.

1.23 Consistency

Where possible, all assessments (clinical, imaging and laboratory) should be performed on the same day. If the dates differ, (e.g. laboratory), please record the different dates on the eCRF. Please note that the actual date of assessments or examinations should be entered on the eCRF, **NOT** the date the eCRF was completed. If the onset of adverse events are reported at a visit and are ongoing, the participant must be asked at the next scheduled visit if the event resolved and if so, the resolution date. This date should then be entered on the relevant adverse event eCRF and in the participant's medical notes.

1.24 Confidentiality

All forms or references to a specific participant outside of the clinical setting must be made using the participant initials, date of birth and Participant Identification number only. On all documents sent outside the site (including to the Project Team), any reference to a participant name must be marked through with a black marker, so that the name can no longer be read. Please ensure that the participant initials, Participant Identification number, date of birth and visit number are recorded on the page before the name is rendered illegible.

1.25 Case Report Forms

Instructions for completing the eCRFs are given in the OpenClinica Site User Manual.

1.26 Submitting eCRFs

It is best to get as much information as possible prior to completing an eCRF page. Once you have entered data onto the eCRF, you will need to submit by pressing 'Save' at the end of the page. It is after the Save button is pressed that any data entry queries will be flagged prior to the data being sent to the EDC. Further instruction is provided in the OpenClinica Site User Manual and will occur at the site initiation visit.

1.27 Study Questionnaires

Most VHCRP studies involve the collection of questionnaire data. Below are listed some common questionnaires used in VHCRP studies.

Refer to the study specific protocol for details of questionnaire completion.

The Behavioural Questionnaires

The questionnaire generally collects information on the following: Demographics; HIV and drug treatment history; Drug and alcohol usage; Injecting risk behaviours, sexual risk behaviours. A screening version and a follow-up version are usually supplied. See Appendix 1 for detailed instructions on how to administer the behavioural questionnaire.

Health Outcomes Survey (EQ-5D)

The EQ-5D health questionnaire provides a simple descriptive profile and a single index value for health status. This information can then be translated into a health utility, which can be used for cost-effectiveness analyses; See Appendix 2 for detailed instructions on how to administer the EQ-5D questionnaire.

Adherence Survey

The questionnaire collects self-reported study drug adherence during the treatment period.

Other

There may be other questionnaires used. Please refer to the study protocol and schedule of assessments for details of which questionnaires should be administered at each study visit.

1.28 Questionnaire Completion

Questionnaires are generally completed on the tablet computer provided to the study site by the Kirby Institute. Alternatively, some studies may allow for online completion through a study website. All questionnaires require a response to every question i.e. null responses are not possible.

The Study Coordinator will be responsible for transferring the data from the tablet to the computer and then sending it on to Project Team at the Kirby Institute.

Paper copies of the questionnaires are provided in the event that the tablet is unavailable. If the questionnaire is completed on paper, please immediately review the survey for any missing responses or questions answered with more than one response.

When questionnaires are completed on the tablet, the questionnaire data must be transferred to your computer every week and forwarded to the study Project Coordinator regularly. Make sure that you back-up the data on a second secure location as well.

If the questionnaires were not done for any reason, please let the Project Team know via email when sending the questionnaires to the study Project Coordinator.

Please contact the Project Coordinator immediately if you have any trouble with the tablet or the data transfer system.

1.29 Using the Tablet Computer and Open Data Kit (ODK)

Turn on and log into the tablet computer, please refer to your study specific tablet instructions for log in information. On the home screen there is the ODK Collect app. Please note that this survey works in Portrait view only.

ODK Collect

1. Tap the **ODK Collect** app (as pictured above).

2. Tap the **Fill Blank Form** button.

3. Tap the **Questionnaires**.

4. A new form will load.

5. Slide the screen forward until you get to the **Participant ID** page. Enter the participant ID in the format 'YYYY-ZZZZZ-###'.
   You will be able to slide to the next screen once this is done correctly.
   TIP: Tap the 'ABC' button to reveal the '-'sign.
   TIP: The program is character sensitive, so don't add any spaces.

6. Enter the **Participant Initials** in the form of 'AA-ZZ'.

7. Enter the **Date of Birth** and slide across.

8. Enter the **Visit Date**.
   TIP: This should automatically show todays date, but just double check.

9. **START SURVEY:** The TITLE screen will appear. You can give the tablet to the participant to complete or assist them with completing the survey.
   TIP: If you need to exit the survey at any time, press the BACK button on the tablet. You can choose one of the following options:

   Save Changes = Saves the survey thus far and returns you to the starting screen.

   Ignore Changes = Does not save the survey and returns you to the starting screen.

   Cancel = Takes you back to your current place in the survey.

10. **END SURVEY:** The THANK YOU screen will appear. Participant will return the tablet to you.

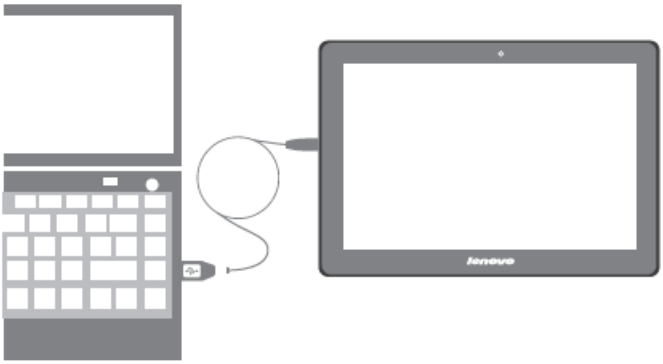
11. Slide forward to the last screen and tap **SAVE FORM AND EXIT.** Once this is complete you will be directed back to the starting screen.

12. In the **SEND FINALISED FORM** button, your saved survey will be added, indicated by a number (i.e. 1= one saved form, 2= two saved forms, etc.).

13. You can add as many forms as you like and these will be saved under **SEND FINALISED FORM.**

14. Once you have finished completing the form, exit ODK Collect.

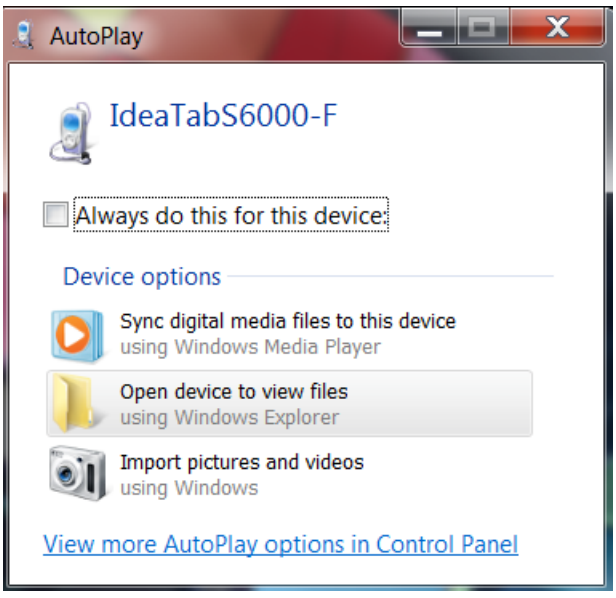
2. Uploading Data From Tablet to Computer



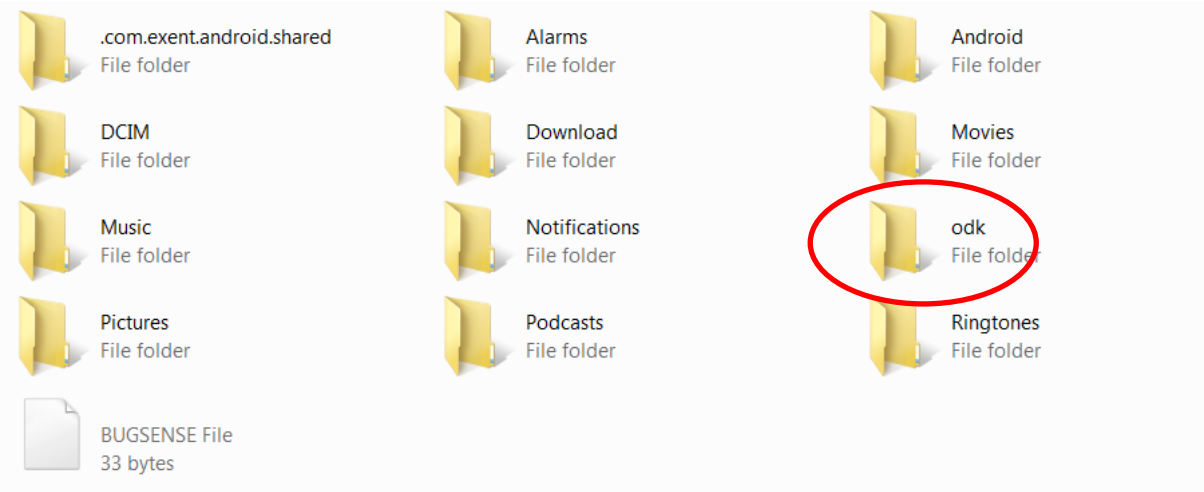
1. Connect the tablet to your PC.

2. Ensure that the tablet is turned on, but ODK Collect is not open.

3. The following screen will appear. Select **Open Device to View Files,** then **Internal Storage.**

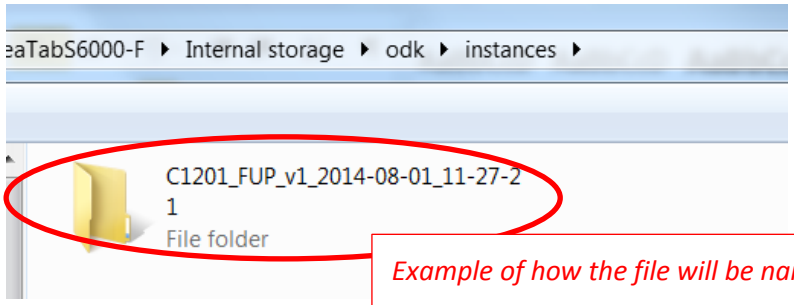


4. Double click on the **odk** folder.



5. Double click the **Instances** file.

6. This folder contains a list of surveys which you have completed, saved by date and time.



Example of how the file will be named.

Subject ID_Visit_Date e.g. 1309-47001-01_Week 2_13-May-15

7. Right-click and copy the file/s that you wish to send.

8. Create a **STUDY Desktop folder** to save a copy of the forms – in case there are problems with email. To create a STUDY desktop folder:

    a. Minimise all open windows so that you are left with a blank home screen
    b. Using your mouse, right click on any blank space of the home screen. This will bring up a dialogue box.
    c. Select new, by using the left clink button on the mouse, then select folder
    d. This will create a new folder on your desktop
    e. Rename this folder to 'STUDY NAME' ODK FILES
    f. Your folder is now ready to paste ODK files into before emailing to the project coordinator

9. Paste a copy in your desktop folder and paste another copy within an email and send it to the Study Project Coordinator.

10. When the email has been received and the attached file checked, you will receive an email to advise you.

3. Sending Data From Computer to Kirby

The files should be nominated as the following:

- Participant ID_Visit_Date e.g. 1309-47001-01_Week 2_13-May-15

The data should be sent monthly to the Project Team at the Kirby Institute either by:

Email: to your study email address: <studyname>@kirby.unsw.edu.au **OR** Cloudstor: the UNSW data transfer system

- **To send by Email**

Enter email address and dates of completed questionnaires in this submission (in message field, e.g. questionnaires from 1 to 7 January 2015). See figure below.

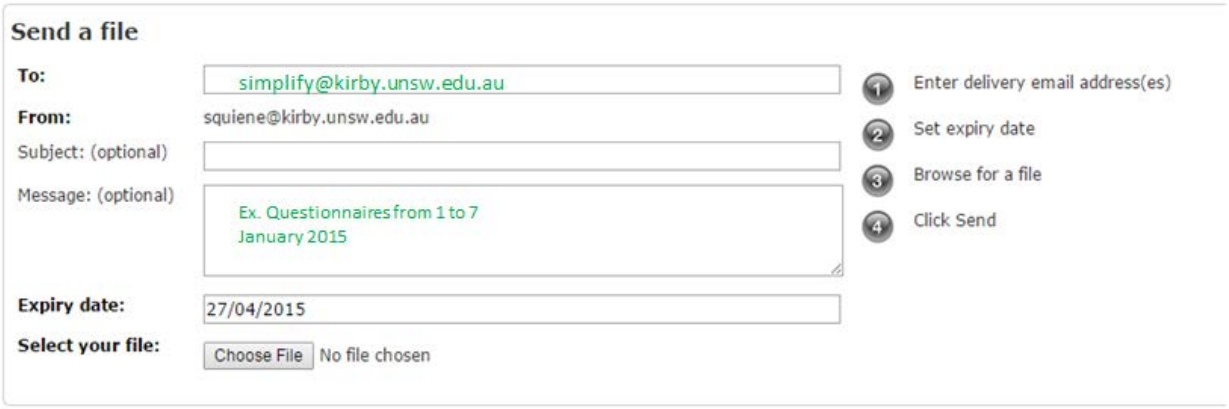


Figure 4 – Data Transfer – By Email

Click on 'Choose file' and select zip file from saved location on computer desktop (or other accessible location).

Click **Send.**

- **To send by Cloudstor**

Go to email account and open latest Cloudstor email from study Project Coordinator requesting questionnaire data.

Dear Sir, Madam,

Please, find below a voucher which grants access to CloudStor.

With this voucher you can upload once one file and make it available for download to a group of people.

Issuer	Voucher link	Valid until
lstevens@kirby.unsw.edu.au	https://cloudstor.aarnet.edu.au/sender/?vid=17e78f38-7b28-b7e9-c309-00001e7481c6	21-04-2015
Personal message from lstevens@kirby.unsw.edu.au:		

Click on voucher link. The voucher is single-use and expires after 3 weeks if unused.

Once done you will receive two messages:

1. **Upload notification**
   "The file below has been uploaded to Cloudstor by <your email address> and you have been granted permission to download this file.
2. **Download notification**
   "The file below has been downloaded from Cloudstor by <kirby study coordinator or data manager's email address>

If a participant declines to answer a question they will not be able to complete that questionnaire on a tablet. They will need to complete a paper version of the questionnaire instead. This allows the participant to skip the question(s) they choose not to answer. The paper questionnaires should be forwarded to the Kirby via the study email address or fax +61 2 9385 9214.

General guidelines for paper questionnaire completion

- Please use black/blue ink
- Ensure the header information is completed on every page
- Except where specified, all questions are single response only
- Please write clearly and legibly
- Comments written extraneously on forms cannot be captured in the analysis; thus, write only in the spaces provided
- If an error is made on a questionnaire, place a single line through the erroneous entry and record the date and your initials. Include the correct response
- Do not skip any items

6. Ethical Aspects and Good Clinical Practice Compliance

1.30 Good Clinical Practice

All clinical research conducted under this protocol is subject to ICH Good Clinical Practice (GCP) Guidelines and will include a site inspection by representatives of the Study Coordinating Centre.

The study will be conducted according to your local guidelines.

Regulatory authorities will approve the study according to local regulation. The relevant Institutional Review Board (IRB)/Independent Ethics Committee (IEC) must approve the protocol in writing prior to the commencement of the study. A statement will be obtained from the IRB, indicating that it operates according to ICH-GCP guidelines or national ethics committee guidelines.

The Kirby Institute requires investigators, study coordinators and other key personnel to complete ICH-GCP training before the site enrolls participants.

1.31 Minimum Consent Requirements

Both the informed consent discussion and the written Participant Informed Consent form and any other written information to be provided to participants should include explanations of the following, where applicable:

a) That the trial involves research.
b) The purpose of the trial.
c) The trial treatment(s) and the probability for random assignment to each treatment.
d) The trial procedures to be followed, including all invasive procedures.
e) The participant's responsibilities.
f) The experimental aspects of the trial.
g) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, foetus, or nursing infant.
h) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.
i) The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.
j) The compensation and/or treatment available to the participant in the event of trial-related injury.
k) The anticipated prorated payment, if any, to the participant for participating in the trial.
l) The anticipated expenses, if any, to the participant for participating in the trial.
m) That the participant's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.
n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.
o) That records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the participant’s identity will remain confidential.
p) That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the trial.
q) The person(s) to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.
r) The foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated.
s) The expected duration of the participant's participation in the trial.

t) The approximate number of participants involved in the trial.

The Project Team will supply an English master consent template (supplied with the protocol) to all sites that are required to prepare an ethics submission. Each site will review the master template, make any modifications required to meet local requirements then return the now site specific consent to the Project Team for review of these changes. Once the site specific version is accepted by the Project Team the final version will be sent for translation (where required). The translated consent is then sent back to site in readiness for the ethics submission. If any amendments are necessary, the site must undertake the checking process again. Deviations from the ICH-GCP guidelines must be justified by a specified, significant and substantial reason, e.g. national requirements.

1.32 Providing Informed Consent and Participant Information

The participant will be required to provide written informed consent before entering the clinical trial in accordance with the related guidelines and regulations.

A copy of the locally approved participant information sheet and consent form must be filed in the Investigator Site File (ISF) and must also be sent to the Project Team. If this document is altered during the study, then the most recent ethics committee approved version is to be used by the Investigator in the consent procedure.

The Site Principal Investigator must ensure that the local ethics committee approved version of the Participant Informed Consent form is used and the original consent form is available for review. On completion of the study, the Participant Informed Consent must be stored with the long-term stored study data. Copies of the originals of the Participant Informed Consent form and participant information documentation should be kept in the Investigator Site File (ISF). If this is not current practice at your site, and if held elsewhere, the location of the original consent documentation should be noted in the Investigator Site File (ISF).

The following procedure for conducting consent is required:

- Each participant is to provide written consent. Each participant must be informed that participation in the study is voluntary and that he/she may choose to withdraw from the study at any time and that withdrawal of consent will not affect his/her relationship with the health care providers. If the participant is illiterate, physically or intellectually challenged, visual or hearing impaired or cognitively impaired, it is important that the study procedures are explained verbally with an impartial witness present, and that both the participant and witness sign the consent form.
- The Investigator should carefully explain to the participant the nature of the study, its purpose, procedures, expected duration and any potential risks or benefits entailed through participation.
- Informed consent should be given by a standard written statement. It should be easily understood by the participant. The consent used must have been approved by the site's Independent Ethics Committee. The participant should be given the time to read and understand the statement before signing the consent.
- The policy of the local Independent Ethics Committee regarding acceptable witnesses must be followed. If deemed necessary by your Independent Ethics Committee, the process of obtaining informed consent should take place in the presence of a witness who is not a member of the investigating team. If present, the witness should sign and date the informed consent form.

- Sufficient time should be allowed for the participant to consider the information, to decide whether or not to participate and to consult, if desired, with their personal physician. The participant must then sign and date the Informed Consent along with the Investigator (and the witness where applicable). The participant should receive a signed copy of the Informed Consent and a copy of the Participant Information. The Investigator should not enrol individuals as participants in the study if adequate understanding of the study and related communications cannot be assured.

If a participant agrees to participate in a sub-study, sub-study procedures may not be conducted until the relevant Sub-Study Informed Consent Form has been signed.

7. Reporting Serious Events and Adverse Events

Not all studies record and report adverse events and serious adverse events.

Refer to the study specific protocol for details of adverse event and serious adverse event reporting.

The following instructions apply if the study requires recording and reporting of adverse and serious adverse events:

1.33 Adverse Events

Adverse events and adverse drug reactions may occur during the course of the study and within the specified follow-up period. These events may also occur in screened participants during the screening period prior to enrolment as a result of protocol-specified interventions.

The definition of an adverse event is any untoward medical occurrence in a participant administered with a pharmaceutical product which does not necessarily have a causal relationship with the product.

Pre-existing conditions or diseases that occur during the study (e.g. seasonal allergies, asthma or recurrent headaches) should not be considered as adverse events unless they change in frequency or severity.

All adverse events encountered during treatment and after drug discontinuation must be reported on the Adverse Event Page of the case report form (CRF). The duration following the end of treatment that adverse events must be reported is detailed in the study protocol.

Laboratory test abnormalities as such should not be reported as adverse events unless they result in a clinically relevant condition or unless the study protocol specifically requires the reporting of laboratory abnormalities.

The Site Principal Investigator or designee must assess each adverse event for Severity and Relationship to study drug. The following categories and definitions are generally used for VHCRP studies however refer to the study specific protocol, eCRF and Serious Adverse Event Form for the definitions and categories for each study.

Severity

Mild:	Discomfort noticed but no disruption of normal daily activity
Moderate:	Discomfort sufficient to reduce or affect normal daily activity
Severe:	Incapacitating with inability to work or perform normal daily activity

Life threatening: Represents an immediate threat to life

Relationship

Unlikely: An adverse event that is unlikely to be related to the use of the drug

Possibly: An adverse event that might be related to the use of the drug

Probably: An adverse event that is likely to be related to the use of the drug

Coding

Adverse events will be assigned preferred terms and categorised into system organ classes according to the Medical Dictionary for Drug Regulatory Affairs (MedDRA) classification of the WHO terminology.

Adverse Events – Good Safety Data Reporting

- Recurrent Adverse Events: in case an adverse event is recurrent throughout the study (e.g. headaches, on and off during the study), report the adverse event on a single eCRF form. Document the start date of the event, and do not enter any stop date until the event is completely resolved. Once resolved, enter the highest grade the participant has experienced.
- When reporting adverse event details, the description of the event should be as specific as possible to prevent any ambiguity.
- The adverse event reporting line should not be used for 'comments'.
- Report a single event on each eCRF form. An example of incorrect reporting is "swelling tongue, throat, face". These events should be broken down into three clear medical concepts; "swelling tongue", "swelling throat" and "swelling face".
- Where a clear diagnosis has been made by the physician, it is not necessary to report the symptoms which support the diagnosis. E.g. if hayfever or seasonal rhinitis is reported; itchy eyes, runny nose, sneezing, hives, itchy skin etc. need not be reported.
- Be specific when reporting adverse events. Take into consideration the location, infectious agent (bacterial vs. viral vs. fungal etc).
- "Pain" is a good example of an event being non-specific. Where is the participant experiencing pain?

Ask the Project Coordinator for further advice on reporting adverse events.

1.34 Serious Adverse Events (SAEs)

The following definition is generally used for Serious Adverse Events however refer to the study protocol and study Serious Adverse Event Form for the definition used for each study

An SAE is any untoward medical occurrence that:

- Results in death;
- Is life threatening;

  (Defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires participant hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is an important medical event

Pregnancy of a participant is often considered an SAE. Refer to the study protocol for details.

All SAEs must be recorded on the study specific paper SAE form and reported to the Clinical Project Coordinator within **24 hours of occurrence** or knowledge of occurrence. SAEs may also often need to be reported to the manufacturer of the study medication. Refer to the study protocol and SAE form for details.

Any additional supporting source documents (e.g. hospital discharge summary, death certificate) must also be provided. If supporting documentation is not available within 24 hours of the site becoming aware of the SAE, then the paper SAE form should be completed as much as possible and submitted within the required 24 hour time period. The supporting documents can be sent when available. Please endeavour to compile and send any supporting documents as soon as possible. The Serious Adverse Event Report Form can be initially sent to Kirby without the site PI's signature to meet the reporting timeline but the form must be signed by the Site PI as soon as possible.

Adverse events classified as "serious" must be recorded on the AE page of the eCRF. When the AE is entered as "serious", an additional paper SAE form will need to be completed.

1.35 Follow-up of Adverse Events and Serious Adverse Events

Adverse events must be followed up at subsequent visits to ensure that all events either resolve or stabilise. Please refer to the OpenClinica Site User Manual for detailed instructions on how to enter updated adverse event information onto the eCRF.

Any Adverse Event or Serious Adverse Event continuing after the protocol defined Adverse Event monitoring period, must continue to be followed up until it resolves or stabilises.

1.36 Special Situation Reports

Some protocols require the reporting of special conditions or other serious medical occurrences.

Refer to the study specific protocol for details.

8. Monitoring and Quality Assurance

1.37 Overview of Monitoring and Quality Assurance

The purposes of monitoring and quality assurance are to verify that:

- The rights and well-being of human participants are protected
- The reported study data are accurate, complete and verifiable from source documents
- The conduct of the study is in compliance with the currently approved protocol / amendment(s), with Good Clinical Practice (GCP) guidelines, and with applicable regulatory requirements.

1.38 Monitoring Visits

Source data verification and monitoring will be conducted as part of this study. There will be an initiation meeting (either on-site or via teleconference), annual on-site monitoring and a close-out meeting (either on-site or via teleconference). The method of monitoring may differ between studies. Please refer to your study specific monitoring plan for more details. Additional monitoring may be conducted if required.

Source documents, including participant medical records, laboratory reports and hard copies of study questionnaires must be available for the monitoring visits. Data entered into the eCRF will be verified by reviewing the source documents.

The Project Coordinator/Monitor will also conduct remote monitoring by reviewing participant data in OpenClinica and any queries will be manually raised in OpenClinica for site review.

The Project Coordinator/Monitor will advise the site of the participants that will be monitored prior to the visit. It is the responsibility of the site coordinator and investigator to ensure the participant files are available to the Project Coordinator/Monitor at the visit. All essential documentation and approval must be obtained prior to commencement of the study, and these will also be checked by the Project Coordinator/Monitor at each visit. All study documentation must be kept for a minimum of 15 years or as per local requirements following the close of the study.

1.39 Documentation for Study Initiation

The Site Principal Investigator should provide the Project Team with the following documents, where applicable, prior to the enrolment of any participants:

1. A letter from the IRB/IEC giving clear approval of the study documents to be used
2. A letter from the regulatory authority giving clear approval, where required
3. A sample of the Participant Information Sheet and Consent Form, as approved by the HREC
4. Signed and dated Site (Clinical Trial) Agreement
5. Signed and dated curriculum vitae (CV) for all Study Investigators, Coordinators and Pharmacists, as available.
6. Site signature and responsibility log
7. Laboratory accreditation certificates
8. Laboratory normal ranges
9. eCRF user activation forms for all Study Investigators, Coordinators and laboratory staff who will enter data on the OpenClinica eCRF and LabKey.

Copies of these documents must be kept by the Investigator.

1.40 Data Verification

As part of the signed Clinical Trial Agreement, the site agrees to allow the Project Team to access the participant files and laboratory results required to ensure correct data entry and to validate data collection. Please note that any site not allowing source document verification will be terminated as a study site and no payment will be made for study-related activities preceding or following termination.

1.41 Study Initiation Meeting

For each site taking part in the study, a study initiation meeting will be held prior to any participants being consented. This meeting will include, where applicable:

1. Instructions on eCRF completion and transmission
2. Instructions on scheduled visits
3. Instructions for the local pharmacy and drug shipment
4. Instructions on blood collection and transport to local laboratory
5. Instructions on specific procedures for the study
6. Instructions on the completion of Serious Adverse Event forms
7. ICH-GCP training.

1.42 Source Documents required at Monitoring Visits

As mentioned previously, the monitor will advise the site of the participants that will be monitored. The chosen participant's medical notes, signed consent forms and pathology results should all be available on the day of the monitoring visits. It is also essential that all documents required in the Investigator Site File (ISF) are up to date at the visit. Where applicable, the documents required in the Investigator Site File (ISF) are listed below:

- Investigator's brochure/Investigational Medicinal Product Dossier and any updates
- Signed protocol and amendments
- Participant information sheet and consent forms
- Any other written information provided to the participant (e.g. newsletters, thank you letters)
- Signed Site (Clinical Trial) Agreement
- Signed Site Indemnity Agreement (if applicable)
- Copy of the regulatory approval
- Ethics information
  - Ethics submission
  - Ethics committee correspondence
  - Ethics committee approval
  - Ethics committee composition, if available
  - Ethics committee updates including reporting of SAEs, annual updates and end of study report as required by the ethics committee
  - Statement of ethics committee compliance with Good Clinical Practice, if available
- Site staff details
  - Curriculum vitae of site staff
  - Specimen signature and responsibility log
  - Training records and certificates (if available)

- Correspondence (any important correspondence with the Kirby Institute or within site staff)
- Site Screening Log
- Laboratory information
  - Laboratory normal ranges and any updates
  - Laboratory accreditation
- Initiation and Monitoring visit reports
- Signed Pharmacy Plan
- Reports of serious, unexpected, drug-related adverse events occurring in any study with the product received from the sponsor.

1.43 Study Close out

Prior to full study completion (and generally when the last recruited participant has completed all protocol mandated procedures or withdrawn – whichever is earliest), a number of activities must be conducted to close out the study. A study closedown visit may be conducted if considered necessary by the Project Coordinator. Commencement of closedown procedures will be defined by the Project Team.

The following activities will be completed, as deemed appropriate by the Kirby Institute:

- All completed Case Report Forms (CRFs) and other data (e.g. questionnaires) will be submitted to the Data Manager for processing and review. Queries raised as a result of data review must be corrected and signed off by the site Principal Investigator or delegate. All electronic data must be uploaded and all outstanding electronic data queries finalised.
- A study closedown letter and site de-registration/closedown checklist will be sent to each site covering the closedown and document retention requirements.
- Site must advise their local ethics committee in writing regarding site protocol deregistration.
- All study supplies must be returned to the Kirby Institute *or* destroyed at site including blank CRFs, laboratory test kits, supplied equipment and any other study-specific tools**.**
- A final report must be sent to the ethics committee and/or regulatory authorities.
- The Investigator Site File must be complete prior to archiving.

9. Specimen Collection and Documentation

Most studies require the collection of research specimens. **Specimens** are the whole blood collected from a study participant. **Samples** are what are stored and used for study endpoints and research after the specimen has been processed e.g. EDTA plasma, EDTA whole blood and PBMCs.

Refer to the study protocol for details of research specimen collection.

1.44 Specimen Collection Time Points

All specimens will be collected in the lab kits provided to the Site Coordinator. Specimens are collected at various time points prior to treatment, through treatment and during follow-up. Samples will be used for central HCV testing and will be stored for future hepatitis C related research.

Refer to the Schedule of Assessments in the study specific protocol for detail for research sample collection requirements.

Each site will have a local sample processing laboratory where the samples will be processed and stored. The local sample processing laboratory will be provided with a laboratory manual outlining the procedures for sample receipt, processing storage and tracking.

During the study, at times determined by the Kirby Project Team the samples will be batch shipped to HepBank, the hepatitis C sample repository located at Kirby Institute laboratory.

Local laboratories will be used for all standard-of-care bloods.

1.45 Specimen Collection Kits

Lab kits will be provided to the Site Coordinator and will contain all the materials required for specimen collection and sample storage at the local processing laboratory.

Screening kits are labelled with a screening ID number starting with a three digit number XXX e.g. 444-024. These kits must only be used for screening visits. If a participant is eligible and is enrolled in the study they will be assigned a participant ID by the Site Coordinator at the Baseline visit (as described in 2.1).

Generally, for most VHCRP studies, each kit (except the screening kit) is labelled for a specific participant and a specific visit.

The Project Team will ensure that sites have sufficient laboratory kits and that materials are within their expiry dates. Replacement tubes will be provided if required.

A sample lab kit is shown in Figure 3 below. Included are blood collection tubes, research sample aliquots tubes, specimen bag, lab request form, aliquot labels, labels for the blood collection tubes and labels for the specimen collection log and a spare label if needed.

Refer to the Schedule of Assessments in the study specific protocol for detail for research sample collection requirements.

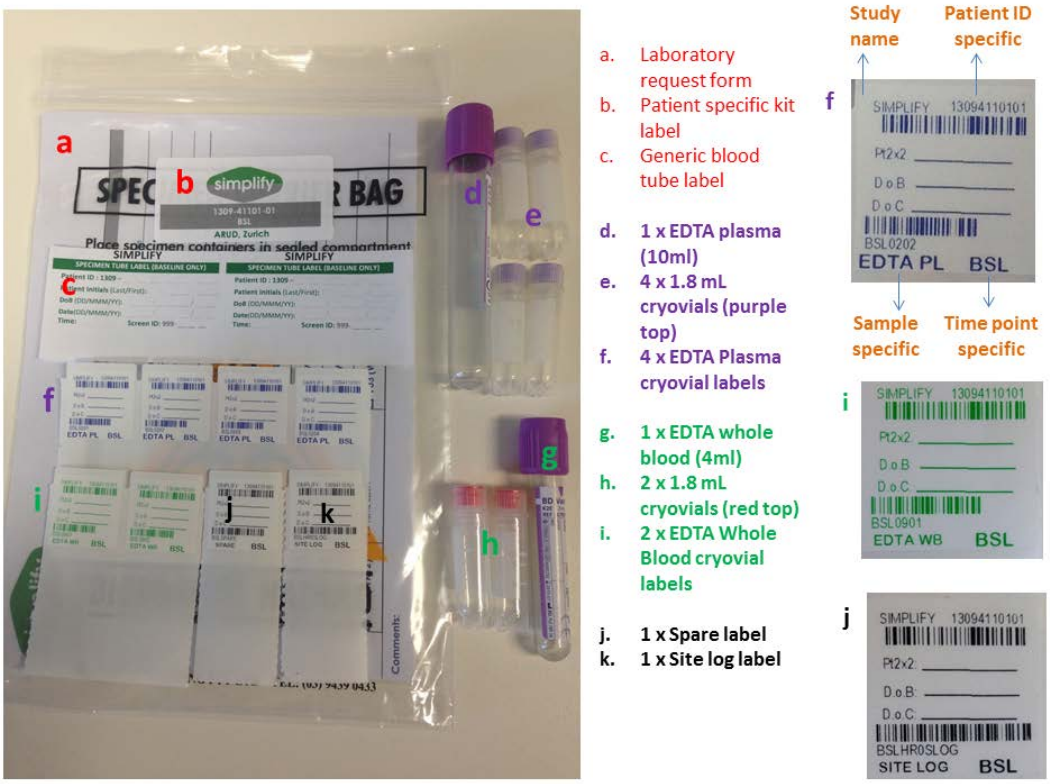


Figure 3: Sample lab kit

1.46 Transport of Specimens to Laboratory

The Site Coordinator will be responsible for delivery of the sample to the laboratory, but the method of transport of specimens to the laboratory will vary between sites. Specimens must be transported safely and securely and in a timely manner.

Most VHCRP studies collect some or all of the samples detailed below. Refer to the study protocol for information on which samples are required.

- **EDTA Plasma**

To be sent to the local laboratory within 24 hours of collection (no batching). Ideally, to be stored at room temperature while waiting for transport, or 4°C if kept overnight.

- **EDTA whole blood**

To be sent to the local laboratory within 24 hours of collection (no batching). Ideally, to be stored at room temperature while waiting for transport, or 4°C if kept overnight.

- **ACD PBMCs**

To be sent to the local laboratory within 24 hours of collection (no batching). Ideally, to be stored at room temperature while waiting for transport, or 4°C if kept overnight.

- **Dried Blood Spots**

To be dried for 4 hours but preferably overnight and then transported to the local laboratory for storage at -80°C or posted to the Kirby Institute. Refer to the study protocol for instructions.

1.47 Specimen and Sample Labelling

Specimens will be collected by the Site Coordinator and transported to the lab.

A. Blood Collection Tube Labelling

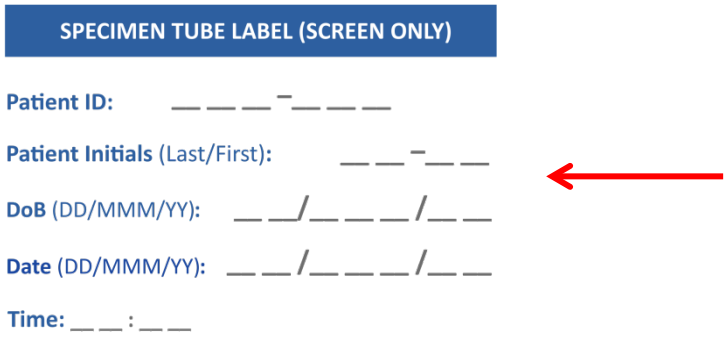
Specimens should be labelled by the Site Coordinator.

Note: There are two types of specimen labels (See figures 4a and 4b below);

a) Screening - the participant is given a Screening ID (XXX-screening number)
b) Visit – the participant is identified by the Participant ID (protocol number -Site number-participant number e.g. 1510-61200-02)

The following visit and participant details should be on the specimen label:

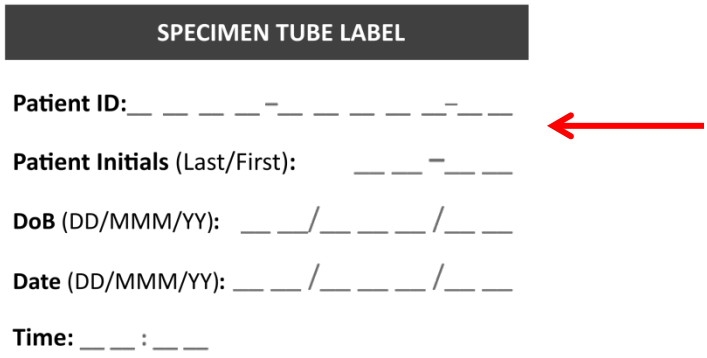
- Patient ID (or Screening ID at screening visits)
- PatientInitials (first two letters of Last Name, first two letters of First Name e.g. Smith, John = SM-JO)
- Date of Birth (DOB) (DD/MMM/YYYY)
- Date of Collection (DD/MMM/YYYY)
- Time of collection



Screening ID

(Starts with XXX e.g. 444-123)

Figure 4a: Screening visit specimen label



Patient ID

(Starts with the protocol number (YYYY) – will be used for all remaining visits e.g. 1510-61201-02)

Figure 4b: Baseline visit specimen label

B. Aliquot Labelling

Aliquot labels are provided for the samples following processing.

The aliquot labels have three very important pieces of information on them as detailed in Figure 5.

- Participant ID
- Visit name
- Sample type

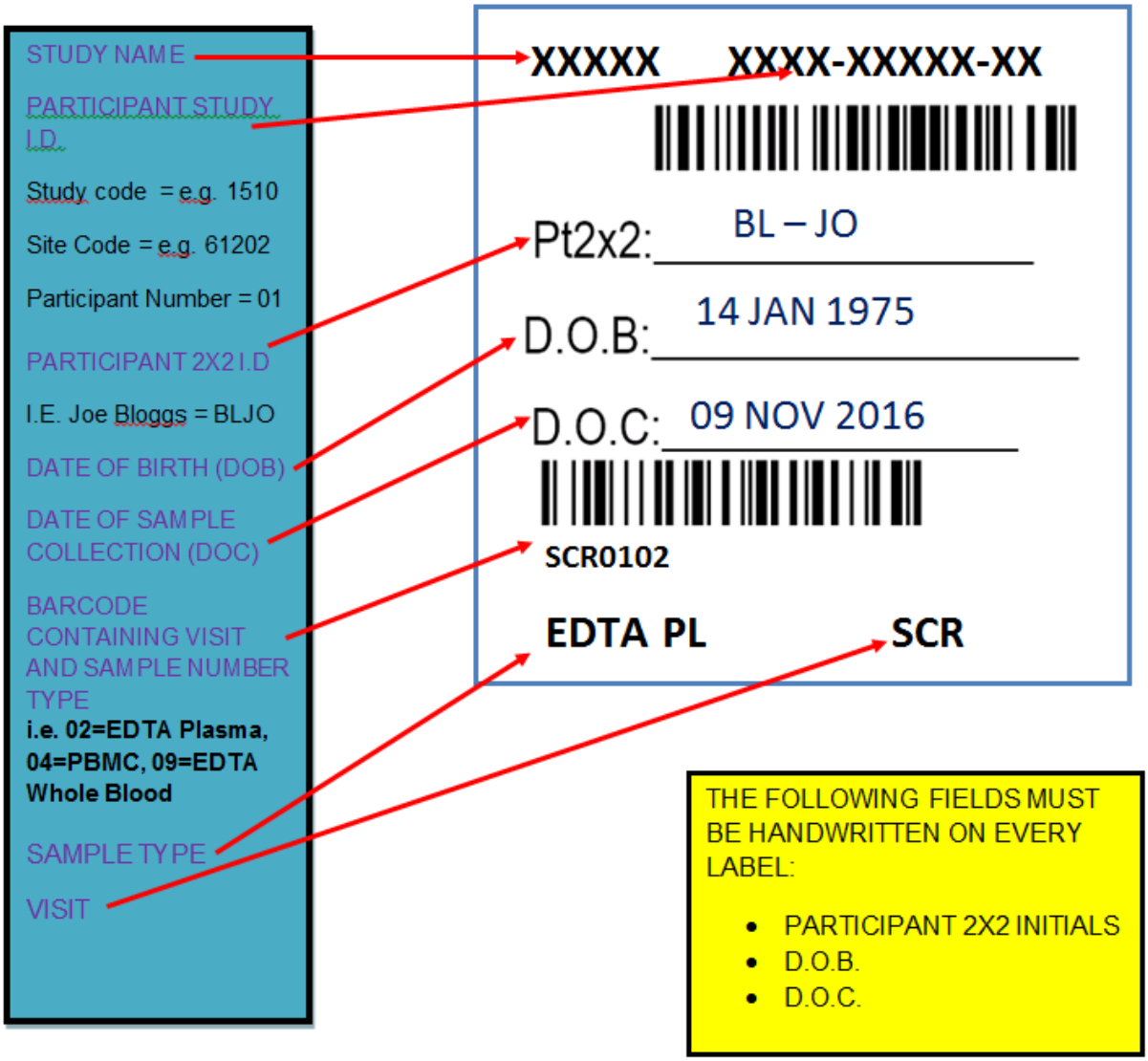


Figure 5: Understanding the aliquot labels

The aliquot labels may or may not be completed by the Site Coordinator. Tubes, aliquots and labels are colour coded to make labelling easier as detailed in Figure 6. You must ensure the correct label goes on the correct aliquot so that we know what is in each aliquot, which participant the aliquot belongs to and which study visit the aliquot relates to.

EDTA plasma from the **LARGE PURPLE** tube goes into the **PURPLE ALIQUOTS** and are labelled with the **PURPLE LABELS.**

Whole blood from the **SMALL PURPLE** tube goes into the **RED ALIQUOT** and are labelled with the **GREEN LABELS**.

PBMCs from the **YELLOW** tubes go into the **YELLOW ALIQUOTS** and are labelled with the **BLACK LABELS**

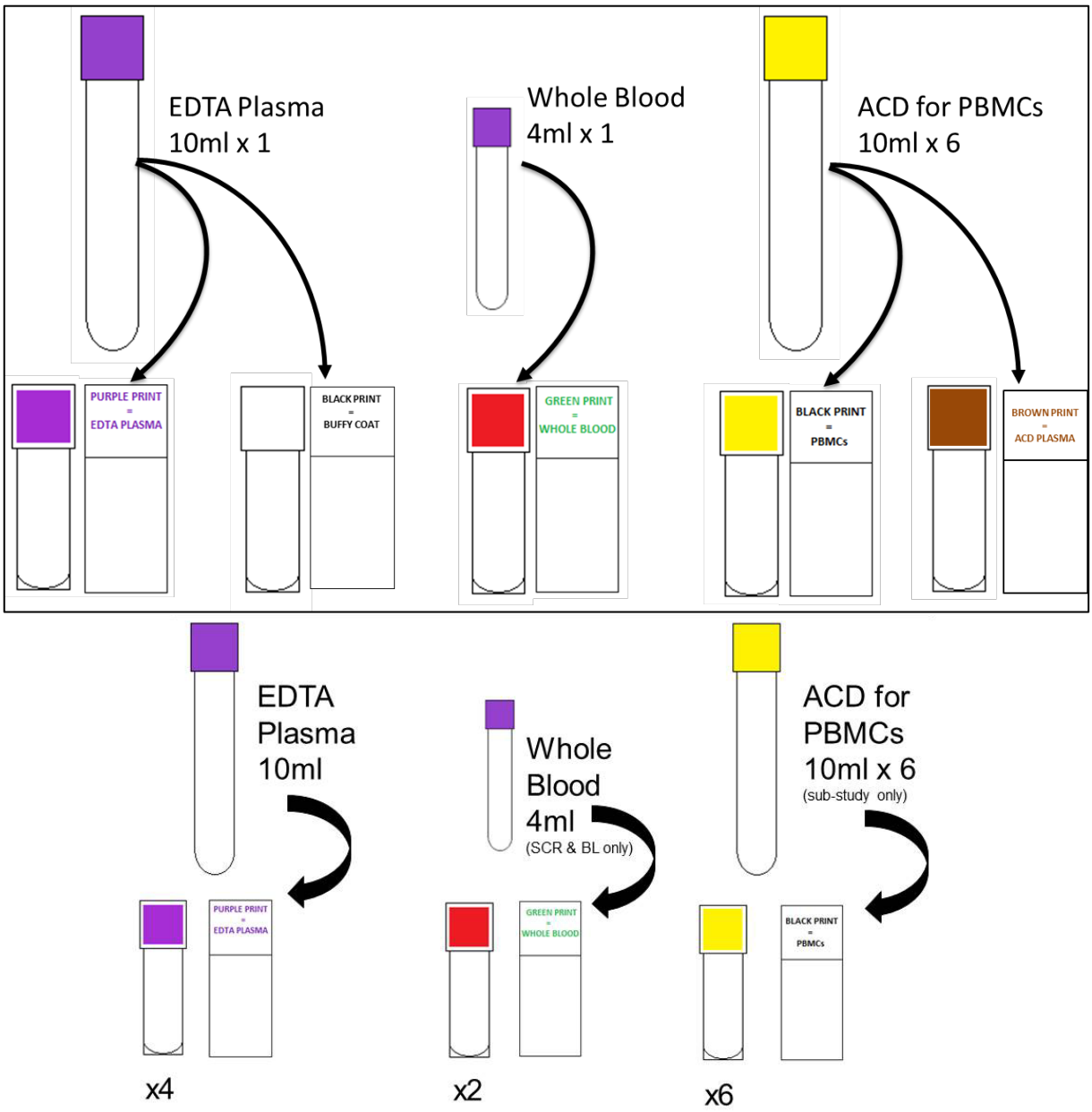


Figure 6: Sample processing and labelling

1.48 **Completing the Laboratory Request Form**

At all study visits the Site Study Coordinator will complete the *Laboratory Request Form* which is a three part (triplicate) non-carbon reproducing (NCR) form. The copies are different colours and should be kept as shown below.

- YELLOW copy remains with the Site Study Coordinator PINK and WHITE accompany specimen to laboratory
- PINK copy to be kept by local laboratory;
- WHITE copy to be sent to the Central Lab (Kirby) at the end of the study and upon Kirby Institute instructions;

The Laboratory Request Form is split into two parts.

a) For clinic use – this will be completed by the Site Coordinator

Details completed by the Site Coordinator are:

- Participant ID
- Participant Initials
- Date of Birth
- Collector's name
- Collection date
- Collection time
- Study visit
- Specimen comments

b) For processing site use only – this is to be completed by the laboratory

Details to be completed by the laboratory technician are:

- Specimen received date
- Specimen received time
- Specimen processed date
- Specimen processed time
- The number and type of samples stored
- Box number and positions of samples
- Confirmation of sample tracking in LabKey
- Sample comments – details of any problems with the samples
- Name and signature of person who processed the samples

Refer to your study specific supplement for the study specific Lab Request Form.

1.49 Sample Tracking

It is an ICH GCP requirement that a log of all specimens collected from participants is maintained. In each lab kit a 'SITE LOG" aliquot label is provided to be stuck onto the Specimen tracking log after the specimen has been collected from the participant.

Refer to your study specific supplement for the study specific Specimen Tracking Log.

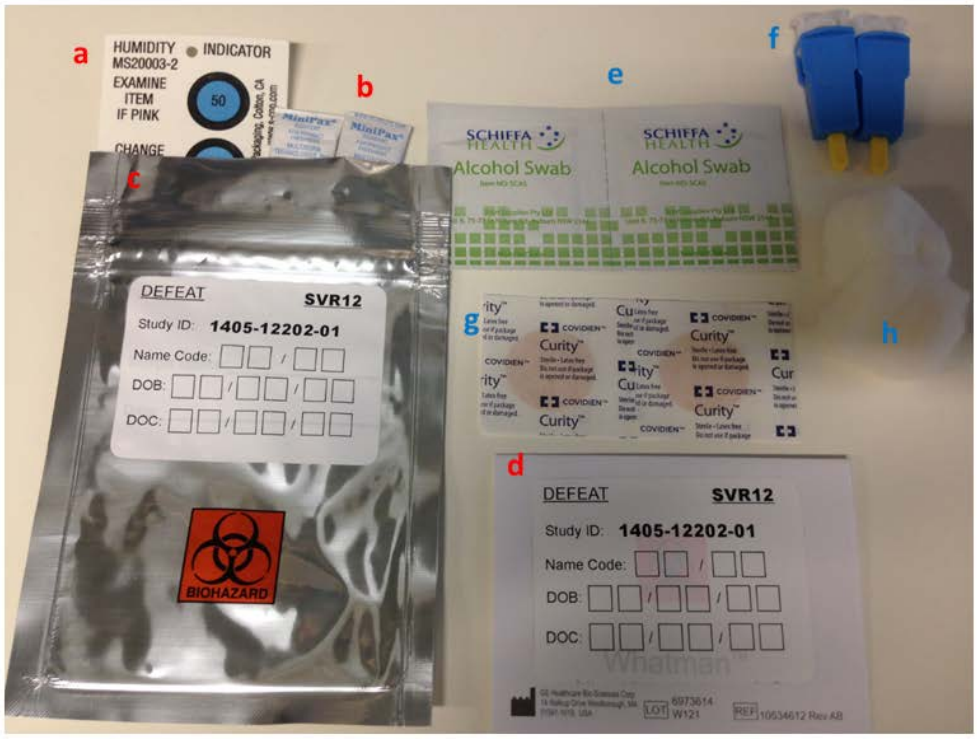
1.50 Dried Blood Spot (DBS) Sample Collection Procedure – DBS Collection Kits

Each site will be provided with a supply of DBS kits. DBS collection kits may be generic or specific for each participant and each visit.

Each kit comprises; (see Figure 7 below)

- Alcohol wipe
- Lancet
- Blood collection card (903 Protein Saver Card)
- Cotton wool
- Band aid
- Foil bag with humidity indication and desiccant packs inside

- If applicable, a label for DBS Collection Log



a. Humidity indicator
b. Desiccants
c. DBS foil bag
d. DBS card

ALL items in RED to be placed inside the foil bag PRIOR to storage.

e. Alcohol wipes
f. Lancets
g. Plaster
h. Cotton wool balls

All DBS Kit contents are placed in a Biohazard Specimen bag.

Figure 6: Example of a Dried Blood Spot (DBS) Collection Kit

Lancets

The lancets provided in the DBS kit are for single use only. As these lancets cannot be reloaded or reused, you will be provided with spare lancets in case of malfunction.

Humidity cards

In the presence of moisture, the nucleic acids of HCV RNA collected on DBS are extremely sensitive to degradation. This means it is essential to ensure the specimens are properly stored. Each foil bag contains a humidity indicator card and desiccant packs to reduce moisture. Please do not remove these from the foil bag at any time.

It is important that the foil bag remains sealed until the DBS sample is ready to post. Please ensure that the foil bag is sealed completely after inserting the sample.

Labels for DBS bag and collection card

Each kit contains labels, which require details to be completed prior to collection of the sample.

Two identical labels are affixed to the:

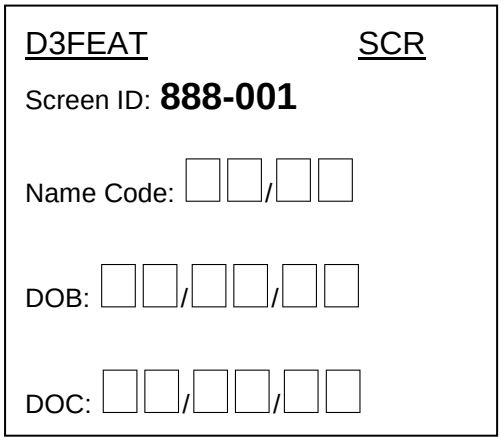
i) Foil bag
ii) DBS collection card

Examples of DBS labels are provided below:

i. **Screening samples**

The Screen ID will be pre-populated so please ensure the correct sample collection kit is used. The remaining fields will need to be completed:

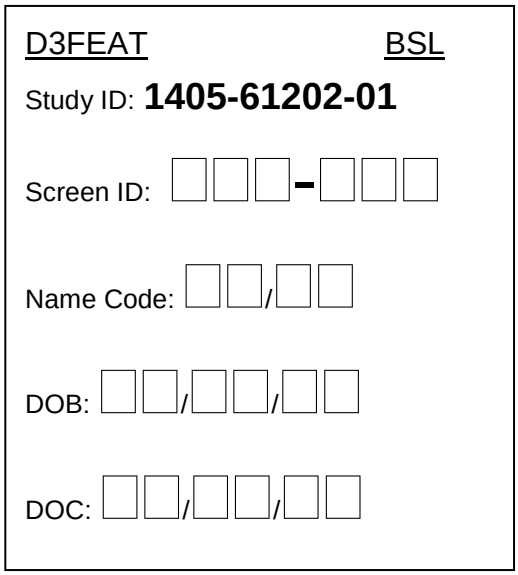
- Pt 2x2 Initials
- DOB
- DOC



ii. **Baseline samples**

The Study ID will be pre-populated so please ensure the correct sample collection kit is used. The remaining fields will need to be completed:

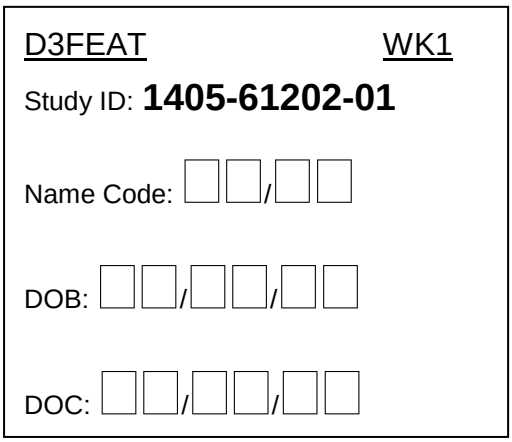
- Screen ID
- Pt 2x2 Initials
- DOB
- DOC



iii. **Week 1 through to FU3 samples**

The Study Visit name and the Study ID will be pre-populated so please ensure the correct sample collection kit is used. The remaining fields will need to be completed:

- Pt 2x2 Initials
- DOB
- DOC



Definitions of abbreviations used:

Abbreviation	Meaning
Screen ID	XXX-XXX allocated at Screening e.g. 444-123
Pt2x2	Participant 2x2 initials = first two letters of **surname** followed by first two letters of **first name**
DOB	Date of Birth. Format: 17/12/62
DOC	Date of Collection. Format: 03/02/14

DBS Collection Procedure

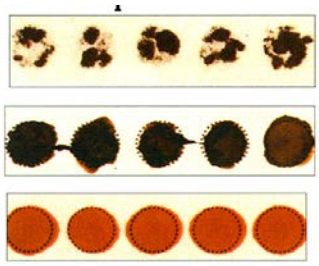
Required Supplies	The contents of each DBS kit is outline in Section 8.5
Preparing to Collect a DBS sample	Always use universal safety precautions: • Treat all blood samples as though they are infectious • Wash your hands • Wear clean gloves for each new participant • Take precaution to avoid needle stick injury • Dispose of contaminated sharps and waste appropriately • Have the card ready and labelled with: - Participant 2 x 2 name code - Participant Date of Birth - Date of collection (dd/mm/yy) **DO NOT TOUCH the DBS collection circles** Please do not submit a card for testing that has not been properly labelled.
Performing a Finger Prick	
	1. Position the hand palm-side up. 2. Choose the fingertip of the ring, middle or index finger; whichever is the least calloused. You can also use the thumb if it is the least calloused finger.
	3. Once you've chosen which finger to prick, it may be necessary to massage the hand and lower part of the finger to help the blood flow to the fingertip.

	4. Clean the fingertip with alcohol. Start in the middle and work outward so as not to re-contaminate the area. 5. Allow the finger to air dry.
	6. Use a new sterile lancet for each participant. Show the lancet to the client so they're reassured that it's new and unused. 7. Place the lancet in the centre of the fingertip.
	8. Hold the finger and firmly press the lancet against the finger when making the puncture.
	9. Dispose of the lancet in a biohazard sharps container.
	10. Wipe away the first drop of blood with a sterile gauze pad or cotton ball. 11. Keep the finger in a downward position and gently massage to maintain blood flow.
How to collect DBS	
	1. Apply gentle pressure to the finger and allow a large, hanging, drop of blood to collect at the puncture site. 2. Working quickly, touch the edge of the drop of blood gently against the filter paper in the centre of the circle, allowing the blood to be drawn into the card by capillary action. *Do not allow the finger to touch the card* 3. Allow another large drop of blood to form at the puncture site and collect this drop in the next circle. Repeat until you have collected enough blood to fill 5 circles on the card. *If the specimen collection is incomplete and no more blood is being produced, the procedure may be repeated on another finger. Five circles must be collected.*

	4. Apply a sterile adhesive plaster over the puncture site.

Important Tips:

- DO NOT press the filter paper against the puncture site.
- Apply blood to only one side of the card
- Do not layer successive drops of blood more than once in the same collection circle
- Do not "milk" the finger, as this can cause haemolysis of the specimen
- Two complete circles are better than five incomplete ones!

	**Valid DBS Specimen** • Each circle is completely filled. • The card has been appropriately labelled. Blood is soaked through to the other side of the card.
	**Invalid DBS Specimens** • Specimen quantity insufficient • Specimen appears clotted or layered • Specimen was not dry before mailing

Drying a DBS sample

How to dry DBS	
	1. Allow the DBS to air dry on a stable surface or on a drying rack for at least 4 hours or preferably overnight. If placed on a stable surface, the flap should be tucked under the filter paper to assist drying. 2. The DBS sample will change from bright red to dark red/brown as it dries. Do not use an external heat source to dry the DBS

Important Tips:

- Avoid touching or smearing the blood spots
- Allow the specimen to fully air dry at room temp
- Keep away from direct sunlight or an open window
- Do not heat, stack or allow DBS to touch other surfaces during the drying process

Transport of DBS to Local Laboratory

How to Package DBS for Shipping

1. Ensure the DBS is completely dry before packing
2. Tuck in the flap of the DBS collection card as indicated. This will protect the DBS from chemicals in the desiccant and humidity indicator.
3. Place card in the provided foil bag. Do not remove the humidity indicator card or desiccant packs.
4. Gently apply pressure to the partially sealed bag to remove as much air as possible before sealing it completely.

No more than one card should be stored in each specimen bag.

How to Store DBS Prior to Shipping

DBS may be kept at ambient temperature in a dark, cool place for up to a week. It is acceptable to store packaged DBS in a box or large envelope.

DBS samples should be sent **once a week** to the laboratory.

1.51 Participant Privacy Protection Warning

UNDER NO CIRCUMSTANCES can personally identifiable information (e.g. real name) about the participant be put on any storage tube, container, label or form that may be seen outside the study site.

Appendix 1: Behavioural Questionnaire

The risk behavioural questionnaire (screening and follow-up) collects participant data on demographics, drug and alcohol usage, drug treatment history, and social functioning.

The questionnaire will take about 20 – 30 minutes to administer and is comprised of four sections: Section A: Demographics, Section B: Drug and Alcohol Usage, and Section C: Drug Treatment History and Section D: Social Support.

Some questions require only a single response to be collected while other questions allow multiple responses. Please pay particular attention to the instructions FOR EACH QUESTION to ensure questions are answered appropriately.

Start the interview by reminding the participant that all the information collected is confidential.

Section A -Demographics

This section consists of demographic questions. Explain to the participant the questions collect general information about them. In the screening version, there are two questions, 'What do you consider the most likely way in which you became exposed to hepatitis C?' and 'What do you consider the other possible ways in which you became exposed to hepatitis C'? The participant should provide only one response to the former question but can provide multiple responses to the latter question.

Section B: Drug and Alcohol Usage

This section consists of questions on drug and alcohol usage including injecting history and injecting behaviour. Drug and alcohol use may predict a number of variables such as who decides to undergo hepatitis C treatment, treatment compliance and hepatitis C clearance and reinfection.

Many people who inject drugs are aware of the risks associated with sharing needles and syringes. As a result the behaviour is somewhat stigmatised so you will need to approach these questions very carefully. To make the participant feel more comfortable about reporting this information you can commence this section by saying:

"We now need to ask you some questions about your drug and alcohol use – when you first used drugs and how often and how you use drugs and alcohol now. These questions will contain information about practices such as sharing needles and syringes and other injecting equipment.

I understand that unsafe injecting happens when a person cannot get new needles and syringes and when this happens you can end up doing things you would not normally do. If anything like this has happened in the last month it is important that you tell us. Remember your answers will not affect your treatment and everything you write down is confidential".

Section C: Drug Treatment History

This section deals with participants' current and past drug and alcohol treatment history. Drug treatment could be a predictor of hepatitis C treatment compliance, HCV clearance and reinfection.

*Section D: Social Support**

This section is about social support. Social support and functioning may influence participants' treatment compliance. The questions in this section are taken from the social function subscale of the Opiate Treatment Index (OTI), which was developed for opiate treatment evaluation.

The scale addresses major aspects of social integration such as employment, residential stability and inter-personal conflict. The scale also provides a measure of social support – the existence of people on whom the participant can rely in times of stress. This will be particularly important for those receiving HCV treatment. The scale also addresses the participants' involvement with the drug sub-culture (whether they are living with people who inject drugs etc.).

When starting this section inform the participant that the questions are about their social life, and that you will ask them about their relationships with friends and family, including how supported they feel. You can commence the section by saying,

"I'm now going to ask you some questions about social support, these include your relationship with friends and family and how supported you feel. We ask these questions because we need to determine how important support is for people being treated for hepatitis C."

You are encouraged to use the following sentences *in italic* to clarify the questions for the participant.

Question 30 - How many different places have you lived in over the last six months?

Include jail, refuges etc as places of residence

Question 31 - How much of the last six months have you been unemployed?

Employment includes full-time work, permanent part-time work, home duties, pension recipients (include *single mother, people with disabilities, etc.) and sex work (if it is legal in the area where the OTI is being administered). Do not include people on unemployment benefits or people on sickness benefits for drug-related problems.*

Question 32 - How many different full time jobs have you had in the last six months?

Include under the term full time job anyone whose usual employment is permanent part-time and the other categories referred to in the above question.

Question 33 - How often in the last six months have you had conflict with your relatives?

Conflict here refers to arguments, disputes, "hassles generally" etc. It is usually helpful to show the interviewee the scale and to let them choose the term that they feel best describes the frequency of conflict they have had over the six months prior to the interview. If the participant has no family or has not been in contact with them in the last six months, circle N/A.

Question 34 - How often in the last six months have you had conflict with your partner(s)?

If the participant has no partner or has not been in contact with them in the last six months, circle N/A.

Question 35 - How often in the last six months have you had conflict with your friends?

Friends in this case refer to acquaintances, as well as close friends. Basically, this question refers to the people the participant "hangs around with". If the participant has no friends, circle N/A.

Question 36 - About how many close friends would you estimate that you have? (INCLUDE PARTNER)

Close friends may be defined as people that the participant feels that they can rely on. If the participant has a sexual partner, make sure they are included in the estimate.

Question 37 – When you are having problems, are you satisfied with the support you get from your friends?

Anything which causes the participant distress can be viewed as a problem e.g. financial, emotional, etc. If the participant is insistent that they do not ask their friends for help, circle N/A.

Question 38 – About how often do you see your friends?

If the participant has no friends, circle N/A.

Question 39 – How many of the people you hang around with now, have you known for more than six months?

If the participant has no friends, circle N/A.

Question 40 – How much of the last six months have you been living with anyone who injects drugs?

Anyone who has injected in the last six months prior to the interview should be considered, for the purposes of the OTI, a drug user. Include both sexual partners and housemates.

Question 41 – How many of the people you hang around with now are users?

This question refers to acquaintances as well as close friends. If the participant has a sexual partner who is a current user, make sure they are included in the estimate. As in the previous question, anyone who has injected in the last six months prior to the interview should be considered a drug user.

*Information is this section (D) is obtained from Darke S, Ward J, Hall W, Heather N and Wodak A, The Opiate Treatment Index (OTI) Manual, 1991, National Drug and Alcohol Research Centre, University of New South Wales, NSW, Australia.

Appendix 2: EQ-5D

This is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression.

The response categories for each of the 5 dimensions are:

1. No problems
2. Some problems
3. Extreme problems

The participant will indicate their health state by placing a cross in the box that best reflects their current health status for each of the 5 dimensions.

EQ Visual Analogue Scale (VAS) (page 2)

This captures the respondent's self-rated health on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

Completing EQ VAS on tablet: The participant is required to enter a number to indicate 'Your own health state today' as it is not possible to draw this on the tablet (Figure 5).

Figure 5. Example of the tablet screen.

Completing EQ VAS on paper questionnaire: The participant is required to draw a line from the 'Your own health state today' box to which point on the scale indicates how good or bad their health state is today (Figure 6, 7).

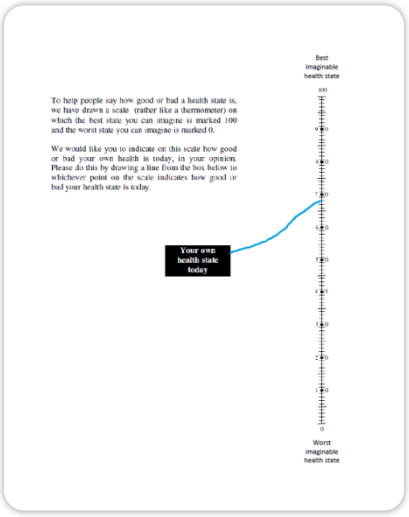


*Figure 6. The **correct** way to complete the EQ VAS*

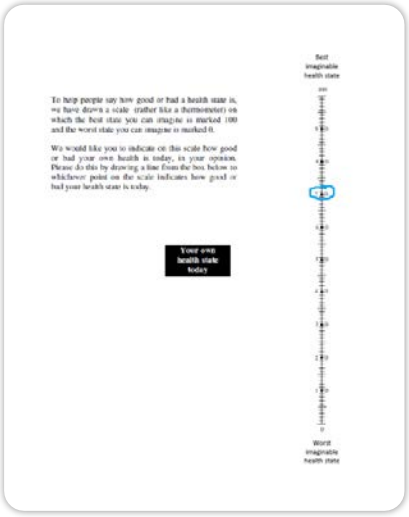


*Figure 7. Example of an **incorrect** way of completing the EQ VAS*

A total score for the EQ-5D is calculated only when all the responses for each dimension are marked. Since missing responses and questions incorrectly assigned multiple responses will affect the validity and usefulness of the scores, it will be useful to emphasise to the participant that it is important to provide a response to each statement in the survey.

After the participant has completed the survey, please immediately review the survey for any missing responses or questions answered with more than one response. The participant should be asked to respond to missed questions or clarify the correct response in these circumstances.