RD&I	NHS University Hospitals Plymouth NHS Trust **STANDARD OPERATING PROCEDURE**

DO NOT USE THIS SOP IN PRINTED FORM WITHOUT FIRST CHECKING IT IS THE LATEST VERSION

The definitive versions of all UHPNT RD&I Dept SOPs appear online, not in printed form, to ensure that up to date versions are used. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the Trust's website: https://www.plymouthhospitals.nhs.uk/researchers

Case Report Forms Design

SOP No: P15

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Page: **1** of **23**

Last Review Date: Jan 2019 Next review date: Aug 2020

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Name:	Chris Rollinson
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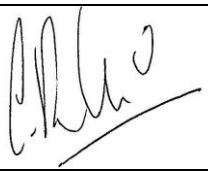
Signature:	
Date:	21st Jan 2019

1 Purpose and Scope

The purpose of this guide is to give assistance in the design of paper Case Report Forms (CRFs). CRFs are the official instrument to collect data from clinical trials and are a key component of quality assurance and control.

CRFs are used to collect data generated for a trial subject, during the course of their participation in a trial. They should be designed to collect data in accordance with the approved study protocol. A well designed CRF also helps to ensure compliance with regulatory requirements. Collaboration with a trial statistician is recommended when designing a study CRF.

Standard CRFs usually include the following forms:

Randomisation/registration form
Entry form (collects baseline data)
Treatment form (doses, AEs, toxicity)
Concomitant medication (if applicable)
Adverse Events & Serious Adverse Events
End of Treatment form (end result of study?)
Follow-ups

In scope: research sponsored by UHPNT, particularly Chief Investigators (CIs), Statisticians, co-researchers, trial coordinators / managers and research nurses.

Definitions

PI	Principal Investigators
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
GCP	Good Clinical Practice
HCA	Health Care Assistants
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
RD&I	Research Development & Innovation

RO	Research Office
SOP	Standard Operating Procedure
UHPNT	University Hospitals Plymouth NHS Trust

2 Who should read this document?

Research staff involved in the designing and implementation of the CRF.

3 Procedure to Follow

3.1 General Principles

Each CRF should be dated and have a clear version number. Any changes to the final CRFs used during a trial should be documented.

The CRF layout should have a logical ordering that follows the schedule of clinic visits and should be consistent with the protocol. Thought should be given in advance as to whether any data collected on the CRF can be validated through monitoring of the original source document if required or if the CRF is the source document.

CRFs should be reviewed and signed off by the Chief Investigator and Trial Statistician, if available before they are used in the trial. It is good practice for data managers, monitors, CRAs and research nurses to view the CRFs prior to sign off as they will have a clear perspective of any practical issues that need to be considered in the capture of the study data.

Ideally a well-designed CRF will remind the Principal Investigators (PIs) at local sites to perform specific evaluations. Research nurses can use it easily to enter data, monitors can check data quickly as the CRF has a logical flow to it, and the database developer will be able to build in edit checks to help with data management and analysis.

The CRF package that is circulated to all local sites should include:

- General instructions
- Use permanent ink when completing
- Complete all items
- Provide glossary of abbreviations
- Contact information
- Procedure for corrections and amendments
- CRF study schedule
- Checklist and section dividers, preferably by visit

3.2 Design Guide

For ease of completion:

- Provide definitions
- Specify units if appropriate
- Avoid requesting unnecessary calculations
- Consider grading visual analogue scales

For ease of understanding:

- Ask explicit questions
- Use absolute questions, e.g.:

Use:	None	Rather than:	Better
	Mild		Same
	Moderate		Worse
	Severe		

- Give constant baselines for comparisons
- Avoid compound questions. This is a question that actually asks several things which might require different answers (more than one question is combined in what seems to be a single question). For example:

  "Are you still taking illicit drugs?" The argument is phrased as a single question requiring a single answer (yes or no), but actually involves two or more issues that cannot necessarily be accurately answered with a single response. By combining the questions "Are you currently taking illicit drugs?" and "Have you ever taken illicit drugs?" it is impossible for someone who has never taken illicit drugs to effectively answer the question, as phrased with a simple "no".

3.2.1 Layout

Keep adequate amounts of free space on the CRF page. Ensure alignment, margins, spacing and fonts are consistent throughout the CRF booklet. Margins should be large enough to accommodate hole punching/binding.

As much as possible, align text to the right with boxes to the left or centred so it is easily understood which tick box is associated to which question:

Layout of CRF should allow for ease of completion, as well as ease of data entry. Things to look for with data entry include adding dropdown choices onto a database, grouping same type of data together on the same form, e.g. dropdown answers together, numeric together and alpha numeric together.

3.2.2 Header

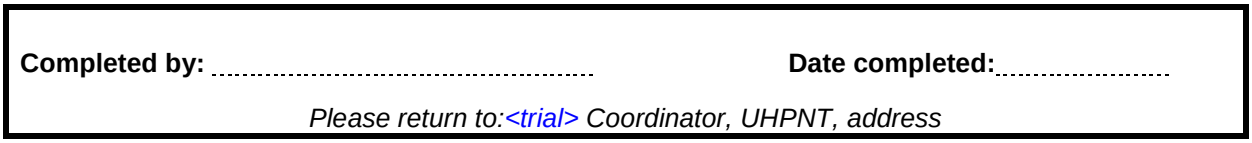
The header of each CRF should include:

- Name of study or study number
- Participant identification number
- Participant's Initials
- Site/centre number (if not included in the subject number),
- Name of form
- If CRF goes to 2 pages, indicate page 1 of 2 and 2 of 2

It is easier to access this vital information when looking through a stack of CRFs if located in the upper right hand corner

3.2.3 Footer

Signatures and dates should be included at the bottom of each CRF. Each CRF should include the address to return form to on the bottom of the form



3.2.4 Data Collection

For data analysis purposes, avoid unnecessary textual data, pictorial data and obtaining data from diary cards. Provide choices for each question, this makes it easier at analysis.

Provide units to ensure comparable values and provide instructions to reduce misinterpretations.

Collect raw data rather than calculated data, e.g. for age, collect birth date and visit date. When collecting toxicity data, it is more valuable to have the exact value of the blood result, e.g. haemoglobin 5.2 g/dl rather than a Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade of 3.

There are different types of data collection responses:

- Open: text, number, alpha numeric
- Closed: Check box, multiple choice
- Combination: open and closed
- Analogue / rating scales

3.2.4.1 Open

Avoid free text if possible as it is almost impossible to analyse. For date / time, add characters to boxes to ensure that the dates are collected in a uniform fashion (DD / MMM / YYYY). This is especially important with international trials.

3.2.4.2 Closed

Provides a list of options e.g. yes/no. Checkbox is the clearest option. If using coding, be consistent across all CRFs, e.g. 'Yes' is always 1, 'No' is always 2.

This is the best choice for collecting and analysing data.

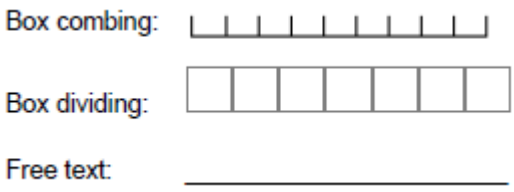
3.2.4.3 Combination

Generally used with closed type questions when one of the possible responses is 'Other', or 'Specify'. This information could be used for future studies as it gives the investigator additional options.

3.2.4.4 Analogue/rating scales

Use only validated instruments, e.g. Quality of Life. They are used to measure one's perception of a situation.

Text boxes should have a consistent design throughout, e.g. utilise box combing, box dividing or free text areas (avoid if possible).



Use a standardised answer mode throughout all the CRFs, e.g.:

Married?	**Yes / No**	**By circling**
Driving Licence?	**Yes / No**	**By underlining**
Any children?	**~~Yes~~ / No**	**By deletion**
Good health?	**Yes ☐ / No ☑**	**By ticking a box**
Do you take regular exercise?	**Yes ☒/ No ☐**	**By cross**
Smoker?	**Yes (1) / No (2)**	**By code**

Tick boxes tend to be the easiest to complete and utilise for data entry.

3.3 Completing CRFs

No fields should be left blank. ND (not done) should be used if data is unavailable either because a measure was not taken or test was not performed. N/A (not applicable) should be used if a measure was not required at the particular time point the form relates to. NK (not known) should be used if the data is unknown and every effort has been made to find the data. CRFs should be signed by all site personnel completing the CRF. The Principal Investigator at the local site is responsible for the accuracy of the CRF.

3.4 Amendments

As a general rule, amendments to data recorded on CRFs should always be handled at the local site. Exceptionally, the Chief Investigator or Trial Coordinator could amend a CRF if this is agreed in writing or verbally AND a copy of the changed CRF is then sent to the local site.

Corrections should be made by drawing a single line through the incorrect item and dating and initialling all corrections. Tippex should **not** be used.

When completing a query, attach an amended copy of the CRF and return either by post or fax to the coordinating centre

3.5 Electronic data capture

Electronic data capture (EDC) will allow the local sites to transcribe subject details direct onto a web-based database, thus saving time and trees. They also offer an advantage as it ensures a standardised format for data entry and can code events. Possible disadvantages include training of staff at local sites to complete online, ensuring that all staff have access to the internet and the need for a paper backup in case of system failure or transcription error and the need to validate computer systems and back-ups.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a Senior RD&I manager***, by the nominated author. These must be ratified by ***a Senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I internet site. Internal Trust Staff are expected to use the RD&I internet site to access latest versions of SOPs and to check the website regularly for updates.

Notice of new or amended procedural documents that have undergone a major amendment will be given *via* the following routes:

- Inclusion in the Trust weekly e-bulletin Vital Signs
- Direct email to Trust Researchers and or teams

4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

CRF template document has been freely provided by The Global Health Network. Please reference The Global Health Network if you use it. www.theglobalhealthnetwork.org

Appendix: Generic CRF template — Appendix 1

Study Code:	Subject study no:				Subject initials:			

This Example CRF can be used as a starting point for designing a study specific CRF. The CRF should include all data which the protocol states will be collected.

CASE REPORT FORM

STUDY TITLE

Insert brief title

Study reference number **insert**

CLINICAL TRIAL SITE/UNIT:

PRINCIPAL INVESTIGATOR:

Subject Initials:			
Subject Study Number:			

I am confident that the information supplied in this case record form is complete and accurate data. I confirm that the study was conducted in accordance with the protocol and any protocol amendments and that written informed consent was obtained prior to the study.

Investigator's Signature: .....

Date of signature:

D	d	m	m	m	y	y	y	y

Study Code:	**Subject study no:**				**Subject initials:**			

Inclusion Criteria		**Yes**	**No***
1	Is the subject a healthy male aged between 18 and 60 years?		
2	Has the subject willingly given written informed consent?		
3			
4			
5			

*If any inclusion criteria are ticked no then the patient is not eligible for the study.

Exclusion Criteria	**Yes***	**No**
1		
2		
3		
4		
5		
6		
7		
8		
9		

* If any exclusion criteria are ticked yes then the patient is not eligible for the study.

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

INFORMED CONSENT

Please note: written informed consent must be given before any study specific procedures take place or any current therapy is discontinued for the purposes of participation in this study.

Has the subject freely given written informed consent? Yes ☐ No ☐

VISIT 1 (SCREENING)

Date: _____
DD MMM YYYY

DEMOGRAPHIC DATA

Age (yrs): | |

Sex: Female ☐ Male ☐

Height (m): | | • | |

Weight (Kg): | | • |

Body Mass Index (BMI = Wt (kg)/H^2 (M): | | • |

SMOKING HABITS

Does the subject smoke or use tobacco products? *Yes ☐ No ☐

***** How many cigarettes per day? | |

Other, specify ----------

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

ALCOHOL CONSUMPTION

Does the subject consume alcohol? Yes ☐ No ☐

If yes, how many units per week? ☐☐

MEDICATIONS TAKEN

Is the subject currently or previously taking any medication including OTC, vitamins and/or supplements? Yes ☐ No ☐

*Record **all** medication on Concomitant Medications page

VISIT 1 (SCREENING)

PREVIOUS MEDICAL HISTORY

Is there any relevant medical history in the following systems?

Code	System	*Yes	No	Code	System	*Yes	No
1	Cardiovascular			9	Neoplasia		
2	Respiratory			10	Neurological		
3	Hepato-biliary			11	Psychological		
4	Gastro-intestinal			12	Immunological		
5	Genito-urinary			13	Dermatological		
6	Endocrine			14	Allergies		
7	Haematological			15	Eyes, ear, nose, throat		
8	Musculo-skeletal			00	Other		

*If ***YES*** for any of the above, enter the code for each condition in the boxes overleaf, give further details (including dates) and state if the condition is currently or potentially active. If giving details of surgery please specify the underlying cause. Use a separate line for each condition.

Study Code: **Subject study no:** | | | | **Subject initials:** | | | |

		Currently Active?	
Code	**Details (including dates)**	**Yes**	**No**

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

VISIT 1 (SCREENING)

PHYSICAL EXAMINATION (to be carried out by medical staff only)

Code	System	*Abnormal	Normal
1	General Appearance		
2	Heart		
3	Lungs		
4	Abdomen		
5	Extremities		

* If ***ABNORMAL*** enter the code for each condition in the boxes below and give brief details. Please use a separate line for each condition.

Code	Details

VITAL SIGNS

Pulse rate | | | | Bpm

Blood pressure (seated) | | | | / | | | | mmHg

ECG

Is the ECG: Normal | | Abnormal | | **

**Description _____

.

Retain signed and dated trace in the plastic sleeve at back of CRF

Study Code: **Subject study no:** | | | | **Subject initials:** | | | |

VISIT 1 (SCREENING)

LABORATORY ANALYSIS **Initials**

Blood for haematology and biochemistry Taken by

✓	Repeat Sample Required?	Date Taken (dd mmm yyyy)
	Haematology	
	Clinical Chemistry	

Please insert a copy of all results in the plastic sleeve at the back of the CRF.

Are all final results: Normal ☐ Abnormal NCS ☐ **Abnormal CS ☐

**Description

Does any result contradict study entry? *Yes ☐ No ☐

Initials:

*If YES, subject must not continue. Please complete off study page.

Add Study Specific Data, as relevant for the particular study

Study Code: **Subject study no:** | | | | **Subject initials:** | | | |

VISIT 1 (SCREENING)

End of Visit Checklist: to be completed by Investigator

		Yes	No
1	Does the subject satisfy the inclusion and exclusion criteria to date?		
2	Have all screening procedures been completed?		
3	Has the concomitant medication page been completed?		
4	Is the subject willing to proceed?		

Investigator

	Yes	No
Is the subject to continue?		
Has medication been collected from Pharmacy?		
Have the dosing instructions been explained to the patient?		

Signature: _____ Date: | | | | | | | | | |

d d m m m y y y y

If '**Yes**' please:

Complete details of next visit and any other needed instructions on the instruction card.

Give the subject the instruction card

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

VISIT 2 (WEEK 1)

Date:_____
DD MMM YYYY

PHYSICAL EXAMINATION (to be carried out by medical staff only)

Code	System	*Abnormal	Normal
1	General Appearance		
2	Heart		
3	Lungs		
4	Abdomen		
5	Extremities		

*** If any changes from baseline, complete adverse event page.**

VITAL SIGNS

Pulse rate | | | | Bpm

Blood pressure (seated) | | | | / | | | | mmHg

LABORATORY ANALYSIS **Initials**

Blood for haematology and biochemistry Taken by

✓	Repeat Sample Required?	Date Taken (dd mmm yyyy)
	Haematology	
	Clinical Chemistry	

Please insert a copy of all results in the plastic sleeve at the back of the CRF.

Are all final results: Normal | Abnormal NCS | **Abnormal CS |

**Description:

Does any result contradict continuation in the study? *Yes | No |

*If YES, subject must not continue. Please complete off study page.

Add Study Specific Data, as relevant for the particular study

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

VISIT 3 (WEEK 26)

Date:_____
DD MMM YYYY

PHYSICAL EXAMINATION (to be carried out by medical staff only)

Code	System	*Abnormal	Normal
1	General Appearance		
2	Heart		
3	Lungs		
4	Abdomen		
5	Extremities		

*** If any changes from baseline, complete adverse event page.**

VITAL SIGNS

Pulse rate | | | | Bpm

Blood pressure (seated) | | | | / | | | | mmHg

LABORATORY ANALYSIS **Initials**

Blood for haematology and biochemistry Taken by

✓	Repeat Sample Required?	Date Taken (dd mmm yyyy)	
	Haematology		
	Clinical Chemistry		

Please insert a copy of all results in the plastic sleeve at the back of the CRF.

Are all final results: Normal | Abnormal NCS | **Abnormal CS

**Description:

Does any result contradict continuation in the study? *Yes | No

*If YES, subject must not continue. Please complete off study page.

Add Study Specific Data, as relevant for the particular study

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

VISIT 4 (WEEK 52)

Date:_____
DD MMM YYYY

PHYSICAL EXAMINATION (to be carried out by medical staff only)

Code	System	*Abnormal	Normal
1	General Appearance		
2	Heart		
3	Lungs		
4	Abdomen		
5	Extremities		

*** If any changes from baseline, complete adverse event page.**

VITAL SIGNS

Pulse rate | | | | Bpm

Blood pressure (seated) | | | | / | | | | mmHg

LABORATORY ANALYSIS **Initials**

Blood for haematology and biochemistry Taken by

✓	Repeat Sample Required?	Date Taken (dd mmm yyyy)	
	Haematology		
	Clinical Chemistry		

Please insert a copy of all results in the plastic sleeve at the back of the CRF.

Are all final results: Normal | Abnormal NCS | **Abnormal CS

**Description:

Does any result contradict continuation in the study? *Yes | No

*If YES, subject must not continue. Please complete off study page.

Add Study Specific Data, as relevant for the particular study

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

VISIT 5 (WEEK 56)

Date:_____
DD MMM YYYY

PHYSICAL EXAMINATION (to be carried out by medical staff only)

Code	System	*Abnormal	Normal
1	General Appearance		
2	Heart		
3	Lungs		
4	Abdomen		
5	Extremities		

*** If any changes from baseline, complete adverse event page.**

VITAL SIGNS

Pulse rate | | | | Bpm

Blood pressure (seated) | | | | / | | | | mmHg

LABORATORY ANALYSIS **Initials**

Blood for U+Es Taken by

✓	Repeat Sample Required?	Date Taken (dd mmm yyyy)
	Clinical Chemistry	

Please insert a copy of all results in the plastic sleeve at the back of the CRF.

Are all final results: Normal ☐ Abnormal NCS ☐ **Abnormal CS ☐

**Description:

Has renal function remained stable? Yes ☐ *No ☐

*If No, record on adverse event page.

Add Study Specific Data, as relevant for the particular study

Study Code: **Subject study no:** | | | | **Subject initials:** | | | |

CONCOMITANT MEDICATIONS

Medication	Total Daily Dose	Units	Reason	Start Date *(MM/DD/YYYY)*	Stop Date *(MM/DD/YYYY)*	Continuing
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐
				__ __/__ __/__ __ __ __	__ __/__ __/__ __ __ __	☐

Study Code: **Subject study no:** | | | | **Subject initials:** | | |

Adverse Events

Has the patient experienced any Adverse Events since signing the Informed Consent? ☐ Yes, specify below ☐ No

AE no.	**Adverse Event** (diagnosis (if known) or signs/symptoms)	**Start Date** dd/mmm/yyyy **and Time** (24 hour clock)	**Stop Date** dd/mmm/yyyy **and Time** (24 hour clock)	**Outcome** 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Patient Died 5=Change in AE 6=unknown	**Severity** 1=Mild 2=Moderate 3=Severe	**Plausible relationship to Study Drug**	**Action taken with Study Drug** 1=None 2=Dose Reduction Temporarily 3=Dose Reduced 4=Discontinued Temporarily 5=Discontinued	**Withdrawn due to AE?**	**Serious AE (SAE)?**	**If SAE does it require immediate reporting? (see Protocol)?**
		/ / :	/ / :			☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No
		/ / :	/ / :			☐ Yes ☐ No		☐ Yes ☐ No	☐ Yes ☐ No	☐ Yes ☐ No

6 Amendment History

Version Number:	2.1
Date Of Amendment:	Jan 2019
Details Of Amendment:	Updated Trust and Dept. name; Reduce signature requirement to single senior RD&I Manager.

Version Number:	2.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	SOP reviewed and updated. SOP numbering system updated.

Version Number:	1.1 (minor amendment)
Date Of Amendment:	Mar 2012
Details Of Amendment:	Cover page - Change of SOP location address.