Also reference SOP011, SOP013, SOP015, SOP041, SOP060 and SOP064

TMF and eTMF Process Guidance Document

Introduction

A Trial Master File (TMF) is the collection of essential documents that are used by Sponsors and Investigators/Sites for the management of a study and by Monitors, Auditors and Inspectors to review and verify whether the Sponsor and the Investigator/Site have conducted the study in line with the applicable regulatory requirements and the principles and standards of Good Clinical Practice (GCP).

In clinical research, essential documents are defined as documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. GCP guidelines list a number of essential documents but it is always expected that a TMF will contain more than just this list, as appropriate to the study and at the discretion of the study team.

The TMF is composed of a Sponsor File, held by the Sponsor organisation and a Site File (also sometimes referred to as the Investigator Site File) held by the Investigator/Site. This is because in organising the TMF it is essential to segregate some documents that are generated and/or held by the Sponsor only, from those that are generated and/or held by the Investigator/Site only (e.g., master randomisation list filed in the Sponsor File only and subject identification code list filed in the Site File only).

The Sponsor File and Site File will be established at the beginning of the study. For a Royal Papworth Sponsored study both a Sponsor and Site File will be set-up. For a non-Royal Papworth Sponsored study only a Site File will be set-up (i.e., the external Sponsor is responsible for maintaining the Sponsor File). In all cases a Working Documents folder will also be set-up but this does not form part of the TMF (see section below).

Paper versus Electronic Trial Master Files

At Royal Papworth Hospital (RPH), unless the Sponsor objects, non-CTIMP studies will have an electronic TMF (eTMF), although some files will still always need to be filed as paper (e.g., wet ink signed consent forms). **All CTIMP studies must have a paper TMF.**

Indexes

- It is good practice for a TMF to follow a standardized index. At RPH we have two indexes, one for Sponsor Files (FRM021) and one for Site Files (FRM068).

- These forms will be reviewed by the study team when the TMF is set-up and any sections that are not applicable to the study can be removed so that the Sponsor and/or Site File index/es are tailored to the study.

- When a new version of FRM021 or FRM068 is released, the study team will review the 'Summary of Changes' tab to check if there are any new folders that would be useful for the study (e.g., new sections or sub-folders that would be of benefit to organize study documents). See below for the process of adding sections or sub-folders from a version uplift.

1.0 Initial Set-up of a TMF (paper or electronic)

1.1 Regardless of whether a paper or electronic TMF is being set-up, an electronic folder for the study will be established on the N:drive:

- If the study has a paper TMF, the electronic folder will be used only as a back up to organise study documents for printing: all essential documents must be printed and filed in the paper files.

- If the study has an electronic TMF (eTMF), these electronic folders will serve as that eTMF and be used as a repository to store all essential documents. There will however be some documents that still need to be stored as paper (e.g., wet ink signed consent forms). Therefore the team will set-up a small paper file for essential documents that need to be filed as paper (see section below).

1.2 The folders and sub-folders of the electronic folder will match the index/es for the Sponsor File and/or Site File as appropriate for the study:

- Use the 'Set-up' columns in FRM021 (Sponsor File Index) and/or FRM068 (Site File Index), to agree as a team which sections of each index are applicable to the study. **NB: It is only expected that a very small handful of sections/files will be marked N/A.** When making this decision it is important to think about whether the section or file will be needed throughout the lifetime of the study rather than just at the set-up stage (e.g., the Publications section may not be applicable at the time of study set-up but may be needed during study close-out/reporting). Files or sections that are definitely not applicable for a study will usually be very obvious (e.g., a Health Economics Analysis Plan will not be needed for a study with no health economics outcomes in the protocol).

- A comment should be added to the 'Comments' column of each index to signpost to any other systems (e.g., OpenClinica, EDGE), if a document is to be stored there instead of directly in the paper TMF or eTMF. This is so that each index provides a 'TMF map.'

- Once agreed, the CPM/RN/CTC or CRA (as appropriate) will approve each index by adding a study version number (i.e., in addition to the template number that is in the footer of each file), together with their initials and the date in the header of the files.

- The final indexes will be saved in both Excel and PDF format in the Sponsor File (Section 0.1, Sponsor File Structure and QC) and Site File (Section 0.1, Site File Structure and QC), respectively. The PDF version allows the 'Day 1' agreed TMF set-up to always be available as a reference and the Excel copy is kept in case of the need to make amendments to the index/es and re-version at a later date.

1.3 Once the indexes are agreed, the team will update the electronic 'Sponsor File' and 'Site File' folder structures on the N:drive so that they match the agreed FRM021 and FRM068 (ie., delete sub-folders that are not applicable). **NB: No re-numbering of electronic folders is required.**

2.0 Initial Set-up of eTMF for a non-Papworth Sponsored Study (SITE FILE ONLY)

2.1 If the study is externally sponsored, send the Sponsor the formal 'eTMF Invitation' letter template (this is a pdf, signed letter on Trust headed paper). **NB: If the Sponsor declines the use of eTMF, set-up a paper TMF but still use the Site File Index (FRM068) for this paper TMF.**

2.2 Use the 'Set-up' columns in FRM068 (Site File Index) to agree as a team which sections of the index are applicable to the study and add comments to the 'Comments' column to signpost to other systems where documents may be stored. Once agreed, the CPM/RN/CTC or CRA (as appropriate) will approve the index by adding their initials, a study version number and the date in the header of the file. The final index will be saved in both Excel and PDF format in the Site File (Section 0.1, Site File Structure and QC). The PDF version allows the 'Day 1' agreed Site File set-up to always be available as a reference and the Excel copy is kept in case of the need to make amendments to the index and re-version at a later date.

2.3 Delete the Sponsor File folder from the electronic folder structure on the N:drive and update the electronic 'Site File' folder structure so that it matches the agreed FRM068 (ie., delete sub-folders that are not applicable). **NB: No re-numbering of electronic folders is required.**

NB: If the external Sponsor sends RPH any Sponsor-level essential documents these should not be filed in the Site File, they can either be discarded or filed for information and reference purposes only, in the Working Documents Folder.

2.4 Set-up a small paper file for documents that need to be filed as paper (see section below).

NB: CTIMP studies will always have a paper Site File regardless of whether they are Papworth or non-Papworth Sponsored.

3 Filing of paper documents

3.1 Only the following documents are expected to be filed as paper for a study with an eTMF:

- Signed Informed Consent Forms
- Study Delegation Log
- Study Training Log
- Site Visit Log
- Screening/Enrolment Log (if maintained as a paper log)
- Signed Protocol Signature page (for all approved versions/amendments)
- Signed Contracts (title page and signature page only)

3.2 The small paper file for these documents will be set-up with a copy of the Sponsor and/or Site File indexes at the front. All documents that are expected to be filed as paper are shown in highlight in these indexes so that for TMF QC and monitoring purposes it is clear what is expected in this small paper file.

4.0 Scanning of documents

NB: YOU DO NOT NEED TO SET UP YOUR OWN SCANNING PROFILE. Please contact Simon Lumley or Tom Devine.

4.1 Any document with a wet ink signature (other than those listed above which are to be filed as paper), needs to be scanned using the validated eTMF scanner.

4.2 Scanning using the eTMF scanner ensures that the scanned copy is a true representation of the original document (known as a certified copy). This allows the original document to be shredded. Although this list is not exhaustive here are some examples of documents that will be scanned and then shredded:

- Completed paper CRFs
- TSC Charter
- IDMC Charter
- File notes
- Protocol Deviation Forms (FRM038)
- Annual Progress Reports (APR) to ethics

4.3 See details and screenshots in Appendix 2 for the scanning process.

4.4 The process for scanning of completed paper CRFs and the timing of destruction of the originals will be agreed on a per study, case-by-case basis. The decision will be documented on the study decision log.

5.0 eTMF QC

5.1 It is expected that the study team performs QC of an eTMF a minimum of three times during the lifetime of a study: once during set-up, conduct and close-out/reporting. This is regardless of whether it is a Papworth or non-Papworth Sponsored study.

5.2 eTMF QC can be completed by any member of the study team.

5.3 Ideally QC will be done before the first monitoring visit for a study.

5.4 FRM021 and FRM068 are dual purpose and will be used to document TMF QC: download a copy of the approved index/es for the study and use the 'QC' columns to indicate whether expected documents are filed or not.

5.5 Once completed, the person performing QC will add their name and the date to the footer of the index and file:

- In the Sponsor File (Section 0.1, Sponsor File Structure and QC) for Sponsor File QC.
- In the Site File (Section 0.1, Site File Structure and QC) for Site File QC.

6.0 Archiving of an eTMF

6.1 When an eTMF study is ready to be archived, all the electronic folders and files must be moved from the R&D PROJECTS area to the R&D PROJECTS ARCHIVE by an authorised member of staff.

6.2 The following minimum paper documents must be archived following the process for paper archiving:

- Signed Informed Consent Forms
- Study Delegation Log
- Study Training Log
- Study Screening/Randomisation Log
- Signed Protocol Signature page (for all approved versions/amendments)

- Signed Contracts (title page and signature page only)

NB: Although the majority of study screening/enrolment/randomisation logs are maintained electronically, it must be archived as paper and the electronic copy deleted. This is because this log will be the only document linking the patient ID to the electronic study data. It therefore needs to be archived separately and not electronically. Print off a copy of the electronic version before it is deleted. The PI will sign and date this paper copy of the log to authorise/confirm that it is the final version before paper archiving.

Appendix 1: GENERAL GUIDANCE

Signposting in the indexes

In reality a TMF will be spread across a number of electronic systems and at the point of TMF set-up any essential documents that will be stored in other electronic systems should be signposted by adding a comment to the comment field of the index. This will avoid the need to copy/duplicate documents between systems. For example:

- OpenClinica for SOPS
- EDGE for CVs and GCP Certificates
- R&D Samples folder for sample logs (until EOS when the final log would be moved into the Site File)

The Working Documents Folder

The purpose of the Working Documents folder is to serve as the day-to-day 'go to' folder for the study and the study team has full control over how this is set-up and what sub-folders are created and used. Essential documents will be drafted here and final Word copies of essential documents (i.e., that are filed as PDF in the Sponsor or Site File) will be saved here in case of the need to make amendments or corrections and re-version at a later date.

Filing Good Practice

- Where possible documents will be filed in an eTMF in PDF format so they cannot be edited.

- Word versions of all documents will be maintained in the Working Documents folder in case of the need to make amendments or corrections and re-version at a later date (e.g., file meeting minutes as PDF in the Sponsor and/or Site File but keep a Word copy in Working Documents so that they can be updated/corrected at a later date if needed and filed in the Sponsor or Site File next to the original version, clearly indicating that these are a corrected version).

- Documents will be filed chronologically, by date of event using the following naming convention:

YYYY_MM_DD_P0 number_Document description_Version number

(Eg. 2016_07_27_P01910_Protocol_Version 14.0)

- Emails will be filed chronologically, by the date of the last email in the email chain, using the following naming convention (i.e., with the word 'email' included after the date):

YYYY_MM_DD_Email_P0 number_Document description

- Emails that have attachments will be grouped into sub-folders within the appropriate Correspondence folder. Attachments will be saved with the same name as the parent email chain plus 'attachment 1 of X' at the end:

YYYY_MM_DD_Email_P0 number_Document description_Attachment 1 of X

Addition of sections or sub-folders due to index version uplift

- When a new version of FRM021 or FRM068 is released, the study team will review the 'Summary of Changes' tab to check if there are any new folders that would be useful for the study (e.g., new sections or sub-folders that would be of benefit to organize study documents).

- If the study team wants to add new sections or sub-folders from a new version of FRM021/68 they will indicate which of the new sections and/or sub-folders are to be added to the TMF in the 'Set-Up' column and save a copy (in both Excel and PDF format) of the uplifted index/es in the Sponsor File (Section 0.1, Sponsor File Structure and QC) and/or Site File (Section 0.1, Site File Structure and QC), respectively.

- When the next QC of the TMF is due, it will be recorded on the uplifted version of the index using both the original agreed index and the uplifted index so that QC includes all sections and sub-folders that are now applicable to the study.

Creation of additional sub-folders

- The guidance notes in the TMF indexes (FRM021 and FRM068) are clear on which sections the study team has the freedom to add sub-folders to (e.g., all Correspondence and Superseded folders). This is for organizational purposes, to allow documents to be filed per topic.

- If a study team feels that the TMF for a study would benefit from additional sections or sub-folders (i.e., that are not permitted per the guidance notes in FRM021/68), this should be raised as a request to the eTMF Committee (Melissa Duckworth or Fiona Bottrill).

Appendix 2: Step-by-step eTMF scanner scanning process

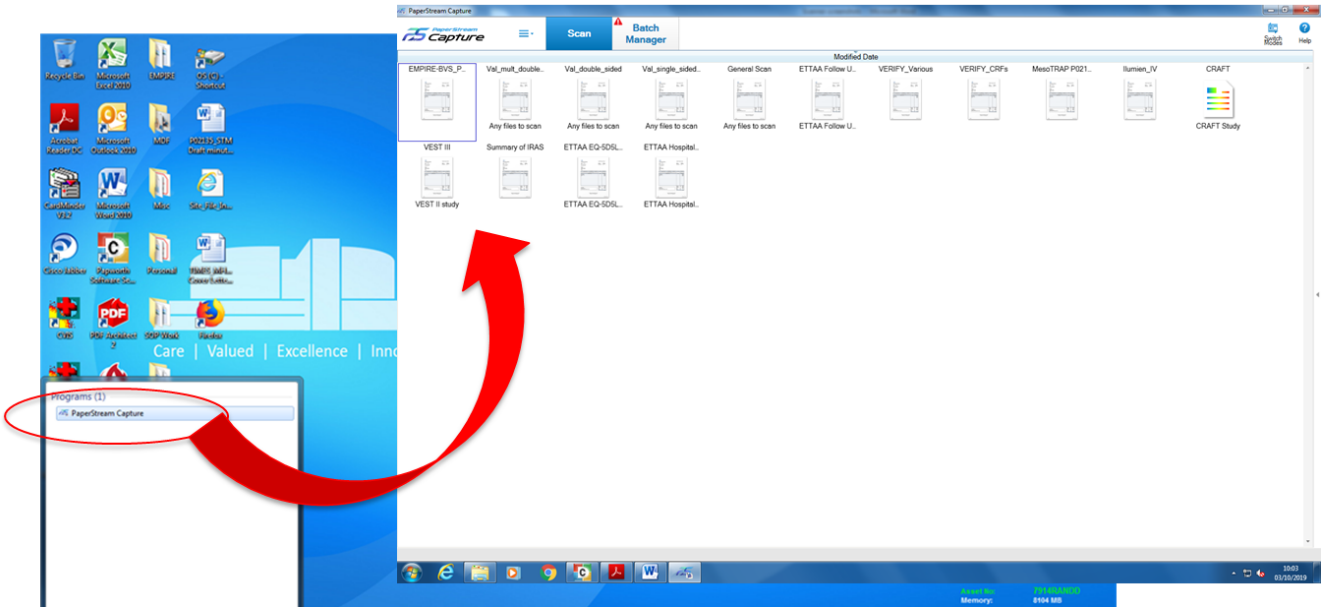
Preparation

- The eTMF scanner (Fujitsu Fi-7140) is located at Royal Papworth House.
- In order to scan documents to the eTMF for a given study, that study must have a 'scanning profile' set-up on the scanner software (PaperStream Capture).
- Please do not attempt to set-up a scanning profile yourself, ask Simon Lumley or Tom Devine to do this.
- A Scanning Log (in Excel format), will automatically be created each time you scan a document and this log follows the document to the destination folder (i.e., there will be a Scanning Log in every folder to which documents are scanned).
- If you scan more than one document to the same folder, an entry will automatically be made on the same Scanning Log (even if documents are scanned at a later date).

Scanning Process

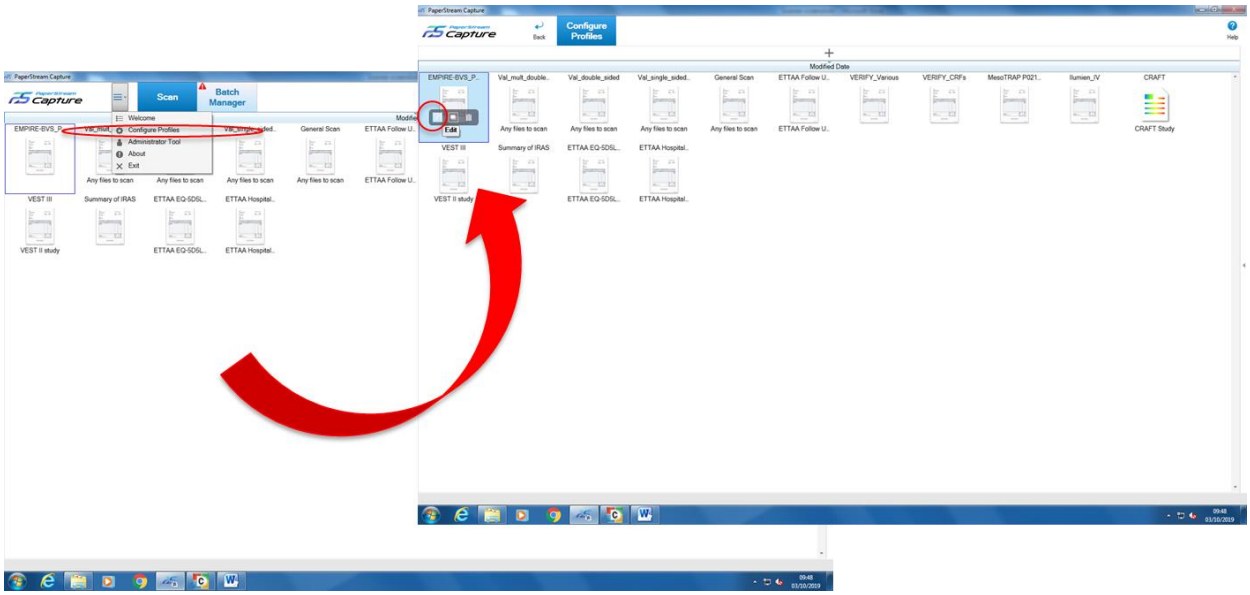
1. Log-in to the desktop computer that is connected to the eTMF scanner with your own credentials (this is to allow detection of who scanned each document for the scanning log).

2. Load the PaperStream Capture program

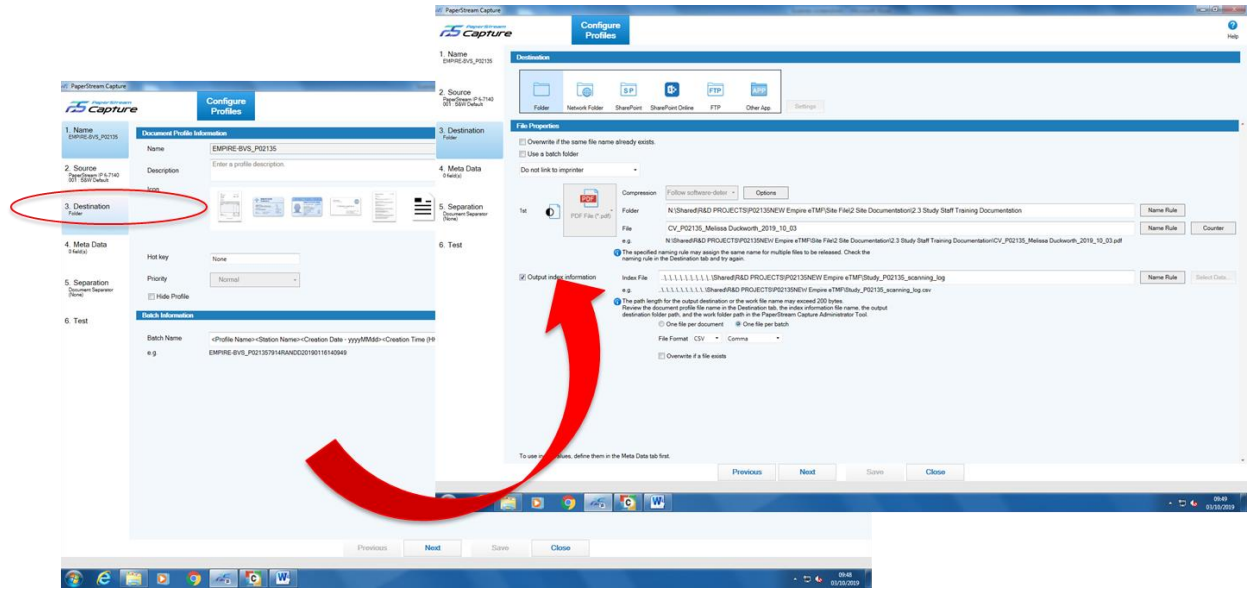


3. From the menu drop-down select ‘Configure Profiles’

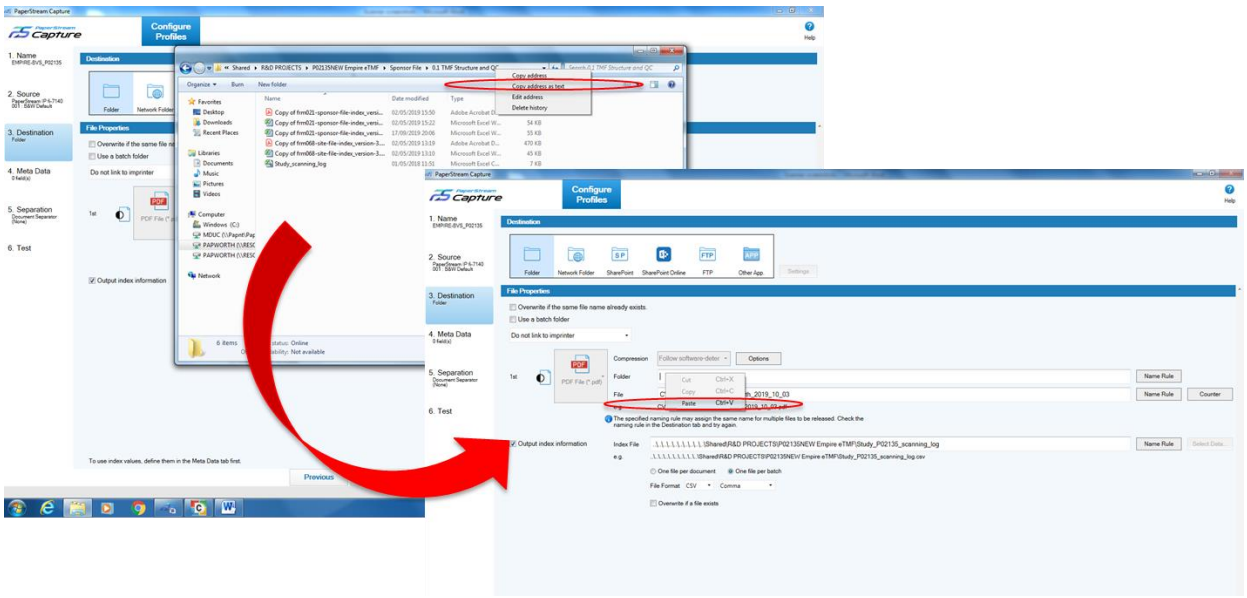
4. Select to ‘edit’ the study profile by clicking on the pencil icon



5. Select the ‘Destination’ tab on the left hand side

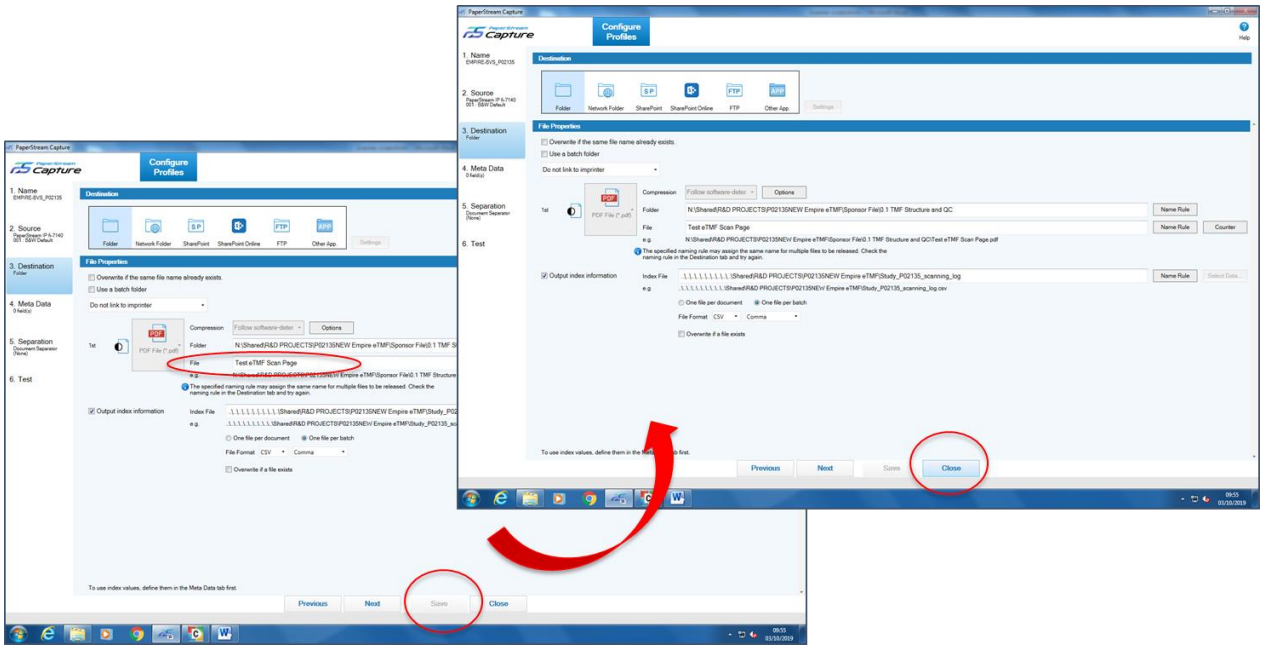


6. In the ‘Folder’ field copy and paste the route to the folder of the eTMF you want to save the document to be scanned (you can do this by right clicking on the folder path as shown)

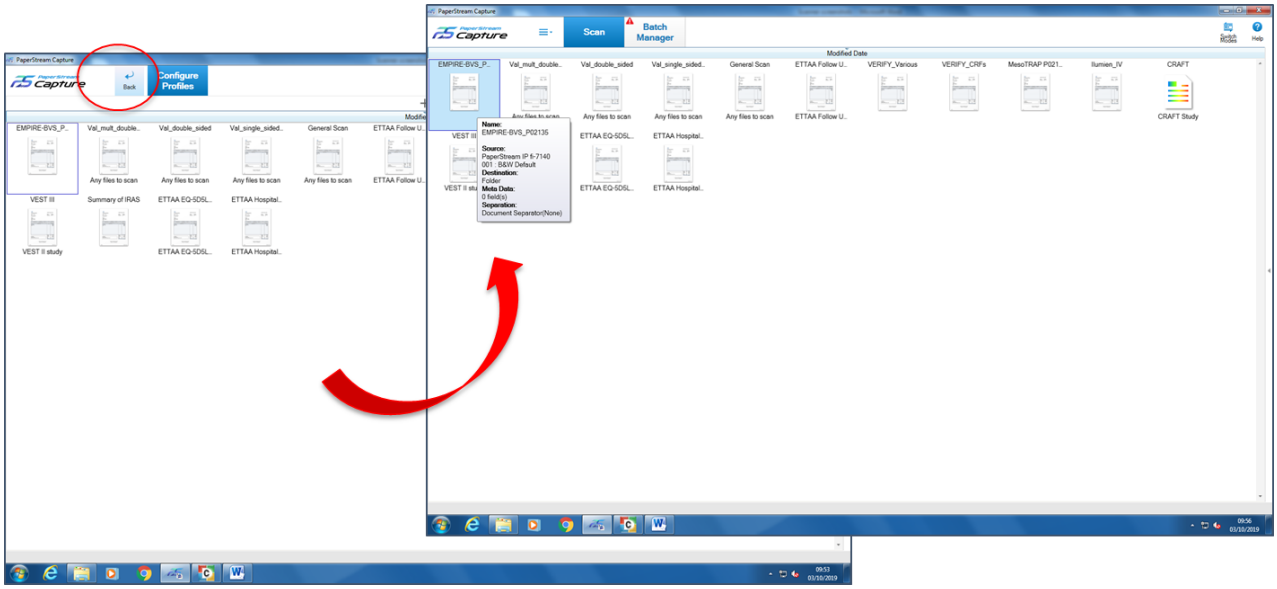


7. In the ‘File’ field type in the name of the document

8. Then click ‘save’ followed by ‘close’



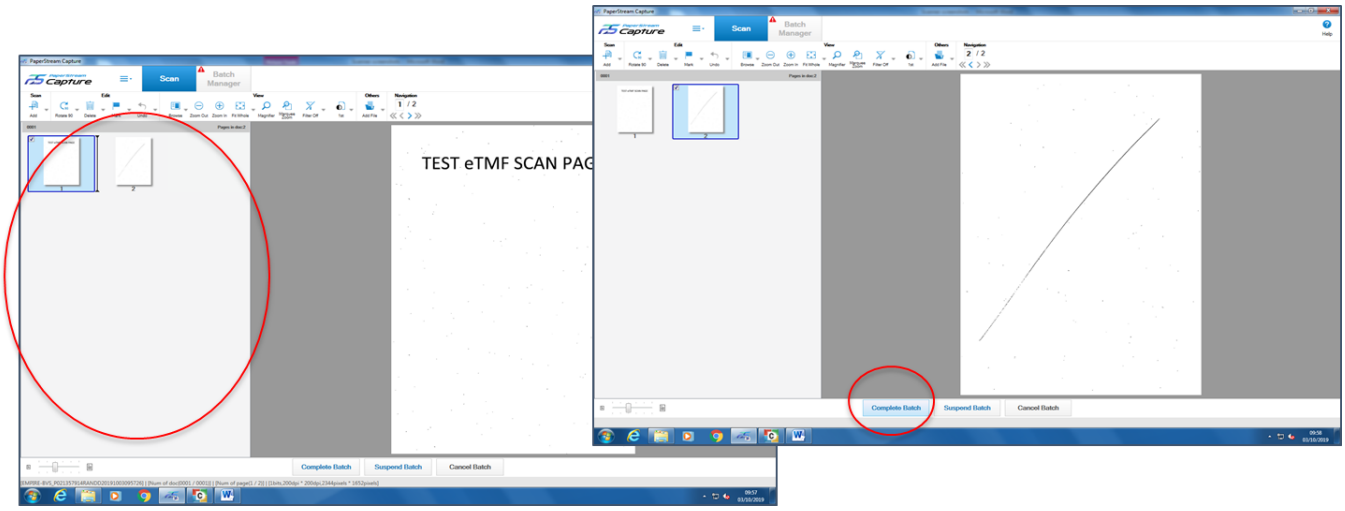
9. Use the ‘back’ button to exit the ‘Configure Profiles’ area and return to the ‘Scan’ home page



10. Place the document to be scanned on the feeder of the scanner (face down, top of document to feed through scanner first)

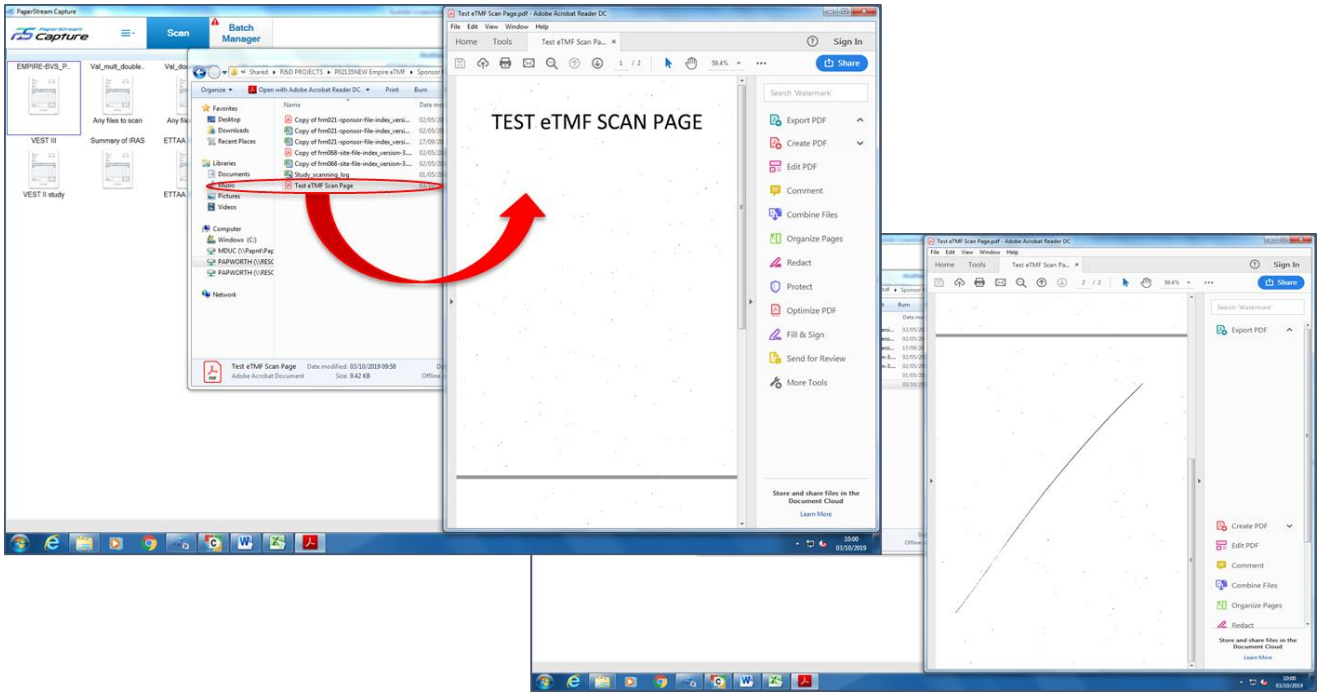
11. Click on the scanning profile for the study (document will immediately be fed through the machine and scanned)

12. Use the left-hand viewing pane to review all pages of the document to confirm they are all present (including blank pages) and verify the scan is a true copy of the original - if so select ‘Complete Batch’



Checks

- The Scanning Log (Excel file), will **follow the scanned document** and appear in the destination folder to which the document has been scanned
- Navigate to the destination folder, open the Scanning Log and check that the document that has been scanned is shown at the bottom of the log (there will be a line for each page, including blank pages)
- It is vital that you **close Excel** after looking at the Scanning Log, as keeping it open will prevent subsequent scans from being recorded in the log
- Navigate to the folder of the eTMF that you intended to send/save the document to and check that it is there and opens successfully



General Scanning Guidance

- Blank pages of documents to be scanned must be marked with a diagonal line across them – this is so that the scanner detects the blank pages and they are easy to review and count.
- If you are scanning a batch of similar documents which the same name except one variable (e.g., CRFs for a number of different patients), there is a tool to allow you to only have to edit the patient number in the file name (please ask Simon Lumley or Tom Devine how to do this as it will save a lot of time!)