MRC Clinical Trials Unit

Smarter Studies
Global Impact
Better Health

UCL

Operational overview – SOPs and trial toolkits

Dr Anna Griffiths

India-UK Networking Partnership Workshop on

Meeting the Challenges of TB Research Priorities in India

Chennai 8-9th Feb 2019/ New Delhi 11-12th Feb 2019

Objectives

- Understand how SOPs are used and developed at the MRC CTU
- What tools and templates are used at MRC CTU to ensure adherence to SOPs

Outline of session

- What is a SOP?
- Understanding the range of SOPs required for clinical trials
- How are SOPs are developed and managed at MRC CTU
- What tool are used at MRC CTU
  - Protocol Development
  - Risk Assessment
  - Trial Documentation
  - Safety Management

What is a SOP?

- Standard Operating Procedures
  - a set of instructions that standardises a procedure or specific function
  - writing down what you do, and do what is written down

Why SOPs are important in CTIMPs?

1 of the 13 core principles of ICH-GCP is:

- Systems with procedures that assure the quality of every aspect of the trial should be implemented.

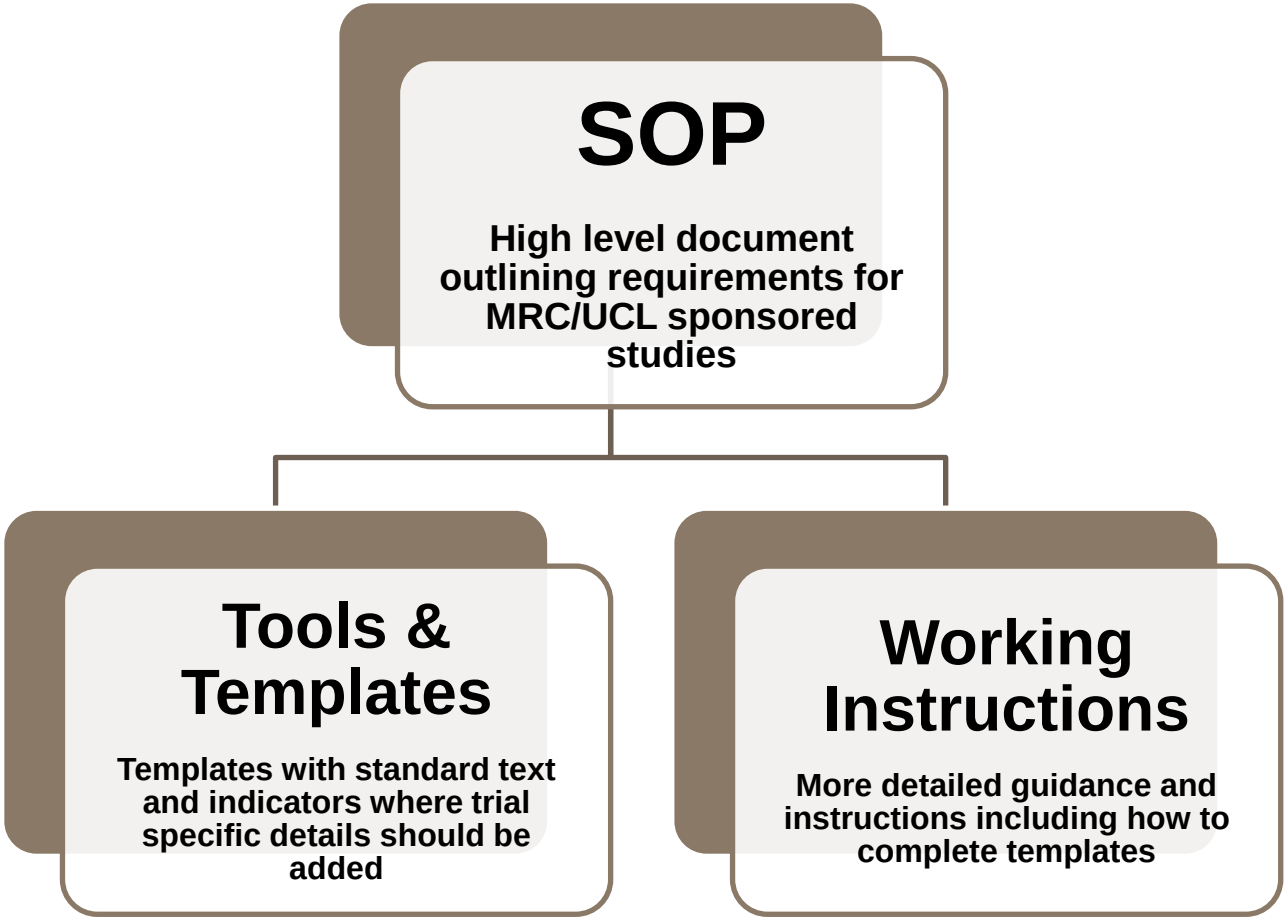
The role of SOPs

- Manage compliance obligations:
  - SOPs ensure that all research conducted as part of the clinical trial follows national regulations, GCP, and institutional policies.
- Create operational efficiency:
  - SOPs ensure processes have been examined and optimised. They standardise common processes amongst all studies.
- Reduce learning curve/training of staff:
  - SOPs are a lifeline to new employees, detailing how activities are required to be performed, they act as a resource to keep everyone on the same page at all times.

The role of SOPs

- Ensure business continuity:
  - SOPs allow for continued operations in the event that a key staff member is unavailable. By referring to the SOP someone can handle an urgent task and do it correctly the first time.
- Quality Control:
  - SOPs help reduce errors, or variations. They improve the quality of the data collected, thereby improving the science of the study.

SOP structure at MRC CTU



How SOPs are managed at MRC CTU

- SOPbox is a document management system
  - ensures version control
  - sends alerts when new SOPs are released
  - tracks when SOPs have been read and understood
  - produces reports to show ‘read & understood’ compliance
  - quiz tests understanding for each SOP

SOP Quiz

- Example from Data Management SOP

What is the definition of the eDC data management model?

Select one:

- ○ Use of paper CRFs which are received by and entered into the study database at the CTU
- ○ Sites entering data directly onto eCRFs in the study database (usually from the patient notes), without recording on paper CRFs first
- ○ Data collected on a paper CRF and then entered on to the study database at a separate location (i.e. not at the CTU)

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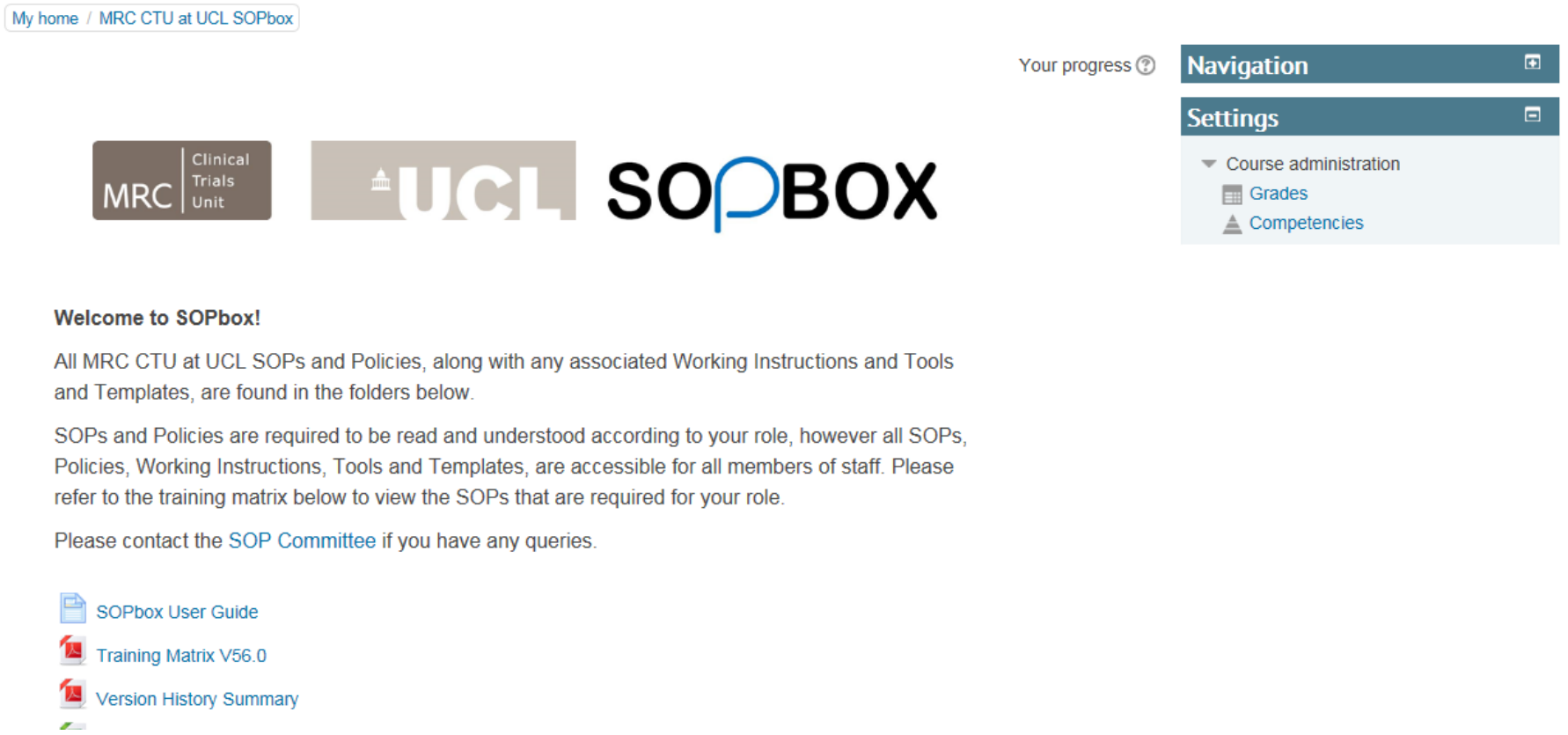
SOPbox

https://moodle.ucl.ac.uk/login/



Who needs to know what?

- A Training Matrix indicates which SOPs should be read by each role within the Unit
- SOPbox is programmed with this Matrix

Document	Version	Release Date	Director—Deputy Director	Programme-Project Lead/ Clinical Scientist/ Research Scientist	COM—CPM	Trial Manager	Data Manager	Trial Assistant	Data Systems Programmer	Data Scientist	Statistics	Methodology	Meta-Analysis	Epidemiology
Blinded Trials - MRC_CTU_SOP_028	3.0	27/03/2018	Yes	Yes	Yes	Yes	Yes		Yes	Yes	Yes			
Clinical Input in MRC CTU at UCL Trials - MRC_CTU_SOP_085	1.0	10/01/2019	Yes	Yes	Yes	Yes					Yes			
Completion of RGC Section in STOPOver - MRC_CTU_SOP_066	1.0	30/07/2015			Yes	Yes	Yes			Yes				
CRF Development and Maintenance SOP - MRC_CTU_SOP_072	1.0	07/01/2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes			
Data Management SOP - MRC_CTU_SOP_009	3.0	15/03/2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	

Creating SOPs

- Author(s)
  - Often more than one person – working group
- Reviewer(s)
  - Often several reviewers from different disciplines
- Approver
  - Head of functional group

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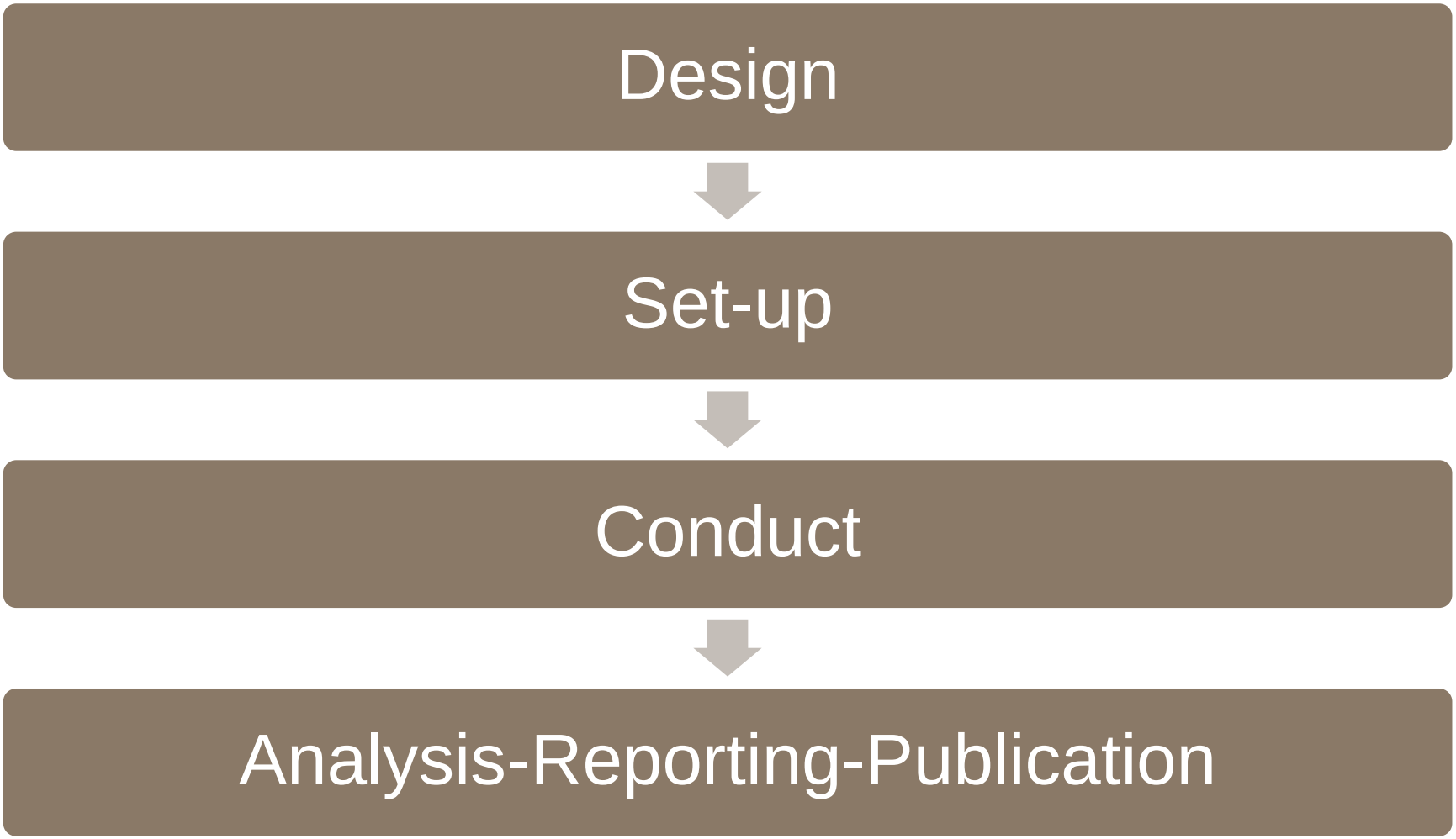
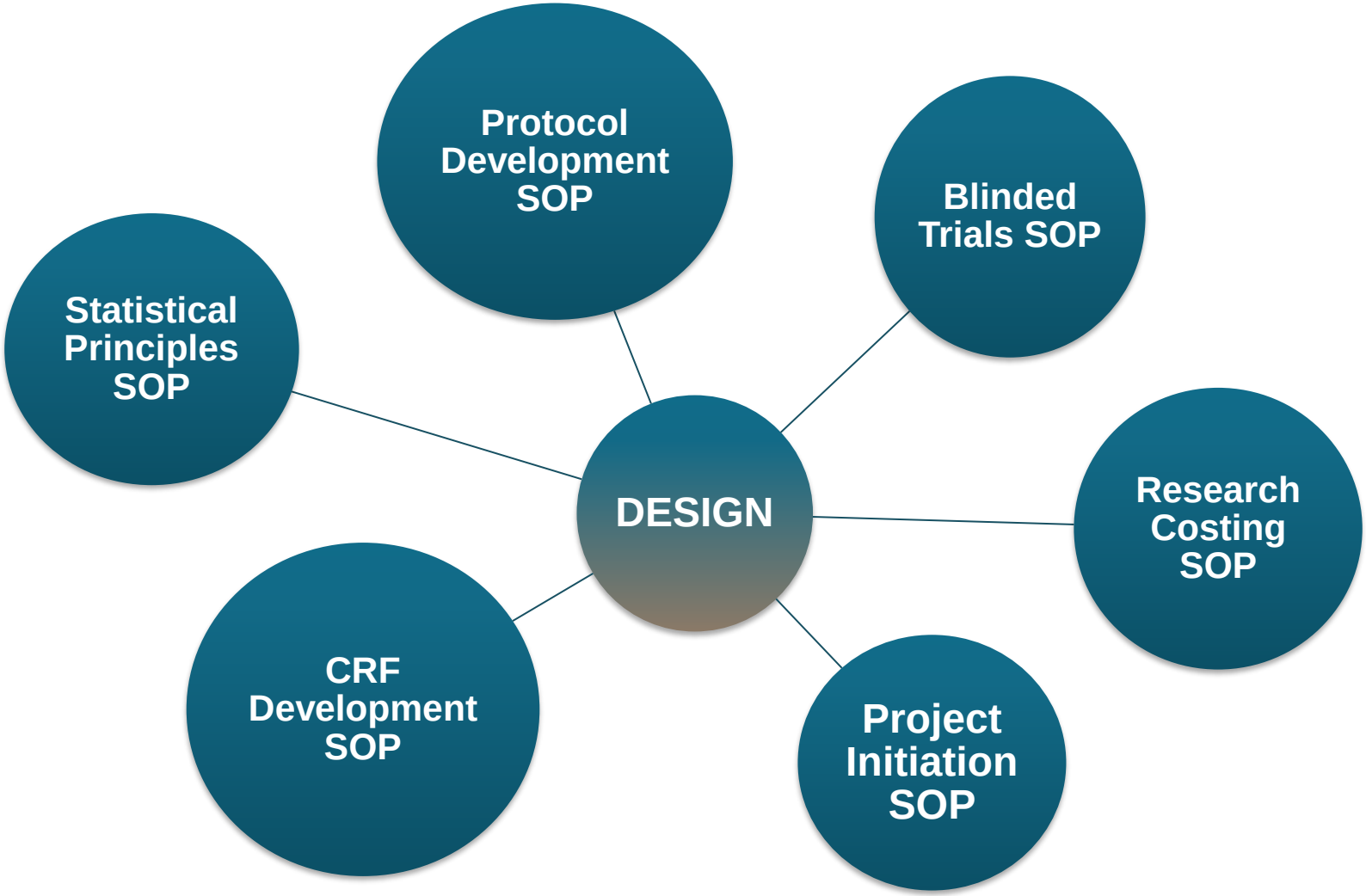
Periodic review to ensure SOPs are fit for purpose and in line with current regulations

Trial Stages



Trial Design



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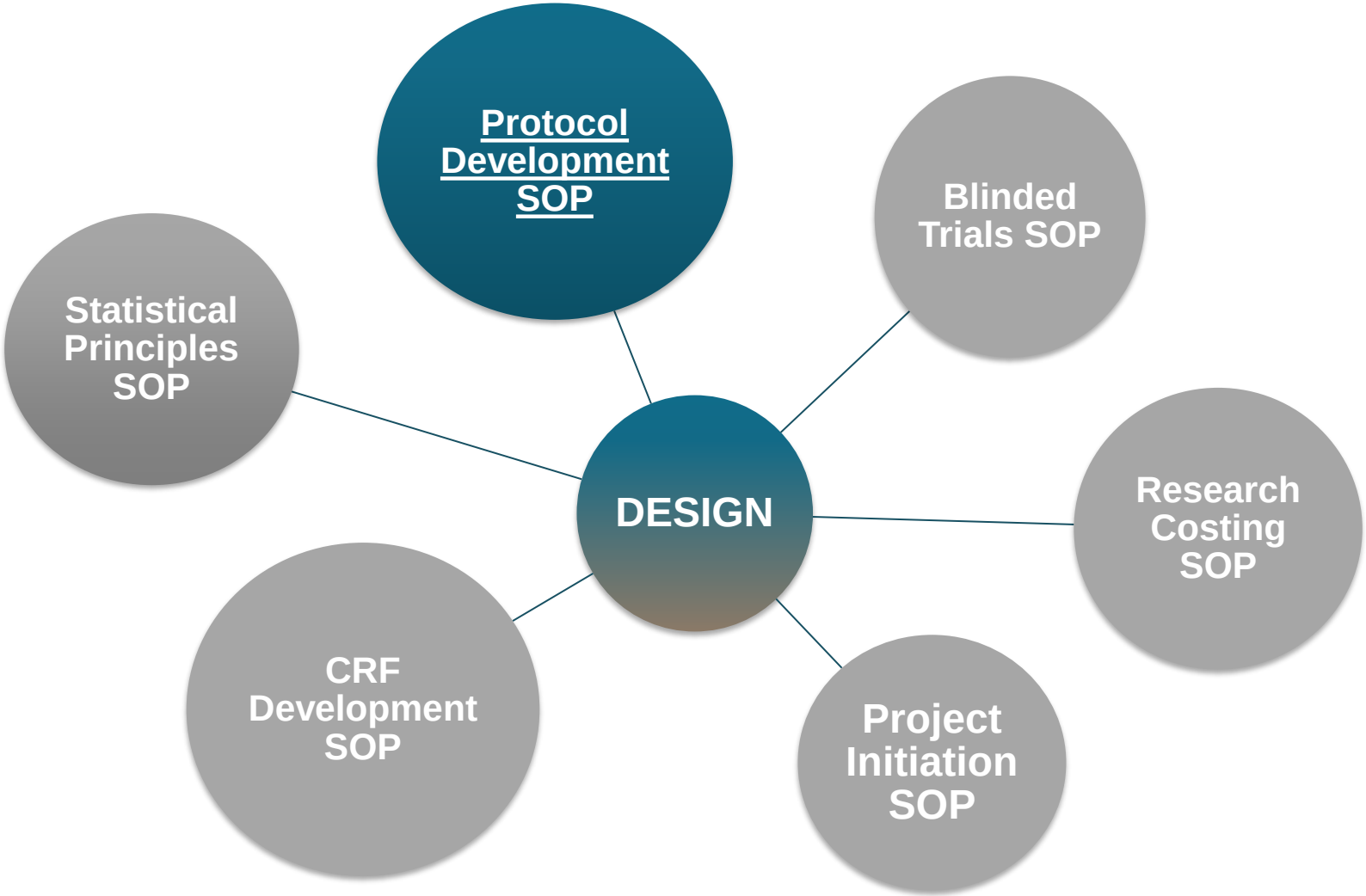


Protocol Development

What the SOP does:

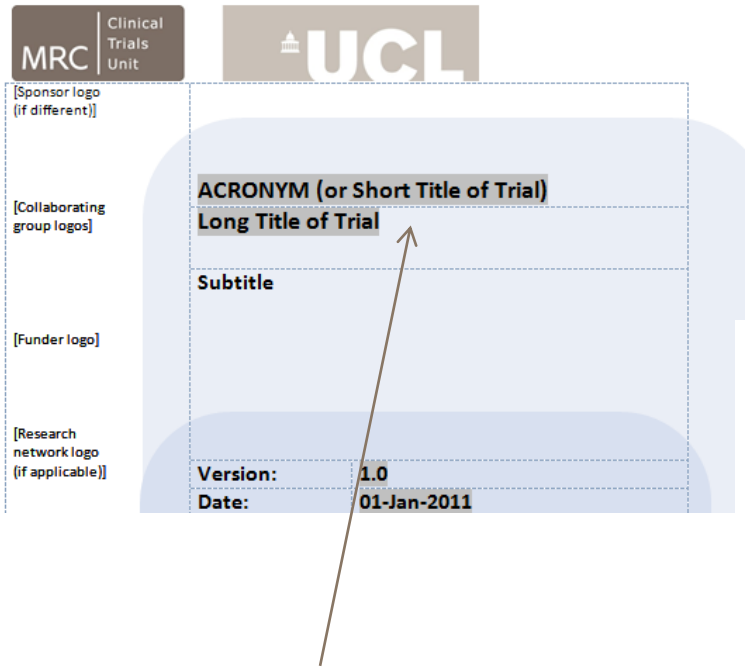
- Outlines the procedures for the development of a Trial Protocol and amendment of a Trial Protocol

- Defines the CTU's roles and responsibilities in respect to local and international regulatory requirements.

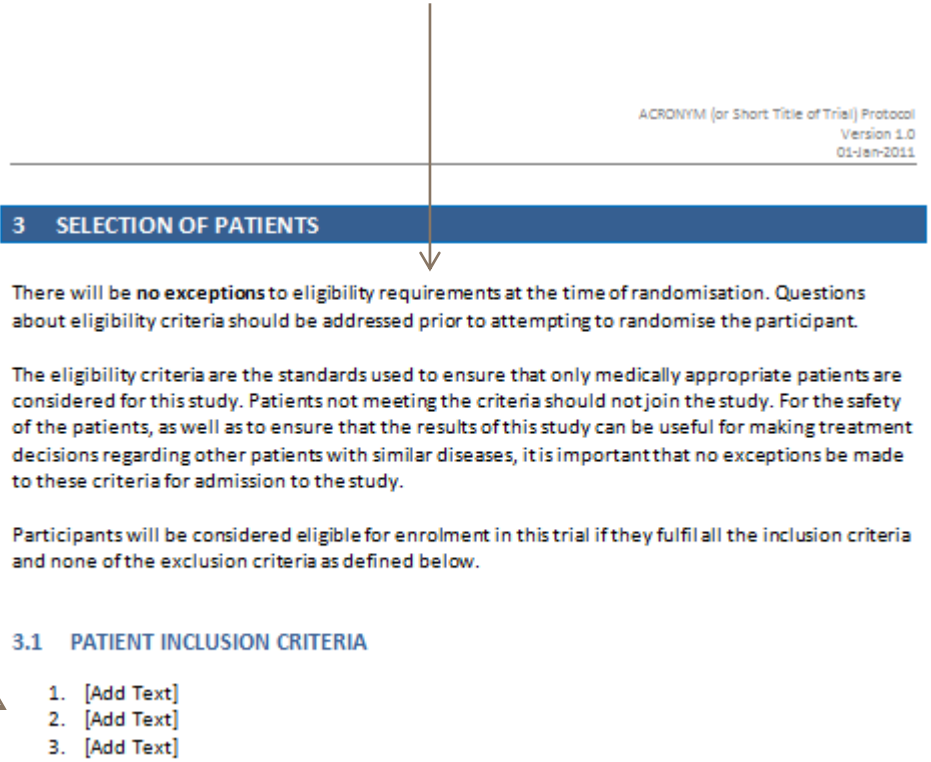
Protocol Template

- Provides the recommended content and format of the Trial Protocol
  - background, objective(s), rationale, design, methodology, statistical considerations, and organisation of a trial
  - must contain all elements required by current regulatory requirements.

Using the Protocol Template



Standard text ensures adherence to Unit SOPs



Indicates where to add trial specific requirements

SURE Trial Protocol

Trial Sponsor

Co-ordinating Centres

Funders

SURE

Short intensified treatment for children with tuberculous meningitis

A randomised trial of 6 months intensified anti-tuberculosis and 2 months anti-inflammatory treatment for HIV-infected and HIV-uninfected African and Asian children with tuberculous meningitis

Version:	1.0
Date:	18 Dec 2018
MRC CTU at UCL ID:	SURE
ISRCTN #:	ISRCTN40829906

Authorised by:

Name:	Professor Diana Gibb
Role:	Chief Investigator
Signature:	
Date	18-Dec-2018
Name:	Dr Angela Crook
Role:	Trial Statistician
Signature:	
Date:	18-Dec-2018

3 SELECTION OF PATIENTS

There should be **no exceptions** to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed prior to attempting to randomise the participant.

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

3.1 PATIENT INCLUSION CRITERIA

1. Age: between 29 days and <15 years
2. Weight: ≥3kg
3. Symptoms compatible with TBM (e.g. fever, vomiting, anorexia, listlessness, headache (see Appendix 6).
4. CSF result with abnormalities compatible with TBM (elevated cell count and/or protein with or without *M. tuberculosis* detected by microscopy or GeneXpert). Physician believes the child needs immediate initiation of anti-TB drugs.
5. Known (or pending confirmation of) HIV status
6. Parent/legal carer give informed, written consent
7. Agree for a CSF sample to be collected and processed for chemistry, microscopy, Ziehl–Nielsen or auramine stain and mycobacterial culture (in process) and, where available, Xpert (Gene Xpert/Rif or Xpert Ultra) prior to commencing treatment or when clinically stable to do so. Where patients have already been started on ATT, pre-screening CSF results should be available.
8. Participant's carer/parent can comply with the protocol requirements in the opinion of the site investigator
9. Home address accessible for visiting and intending to remain within the recruitment area for follow up period of at least 18 months

Trial Set-up


Ethics Committee SOP
Drug Supply Management SOP
Database Development SOP
Trial Set-up
Sponsorship SOP
Research Contracting SOP
Trial Management SOP
Risk Assessment SOP

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Risk Assessment

- The potential hazards, the consequences of those hazards, and for each hazard identified the risk, i.e the likelihood of adverse consequences and their impact, should be considered.
- For each hazard identified, risk reduction strategies should be considered.
- The SOPs and Policies in place are designed to manage the standard risks.
- RA reviewed by Research Governance Committee

Risk Assessment - categories

The safety and rights of participants

- Nature of the Intervention
- Invasiveness of clinical procedures
- Vulnerability of patient group
- Data Protection and security

Project design and reliability of results

- Aspects of design that may impact reliability of results
- Use of data for product licensing
- Data collection methods

Project management and governance

- Sponsorship arrangements
- Oversight arrangements
- Organisational complexities

Other considerations

Trial Set-up


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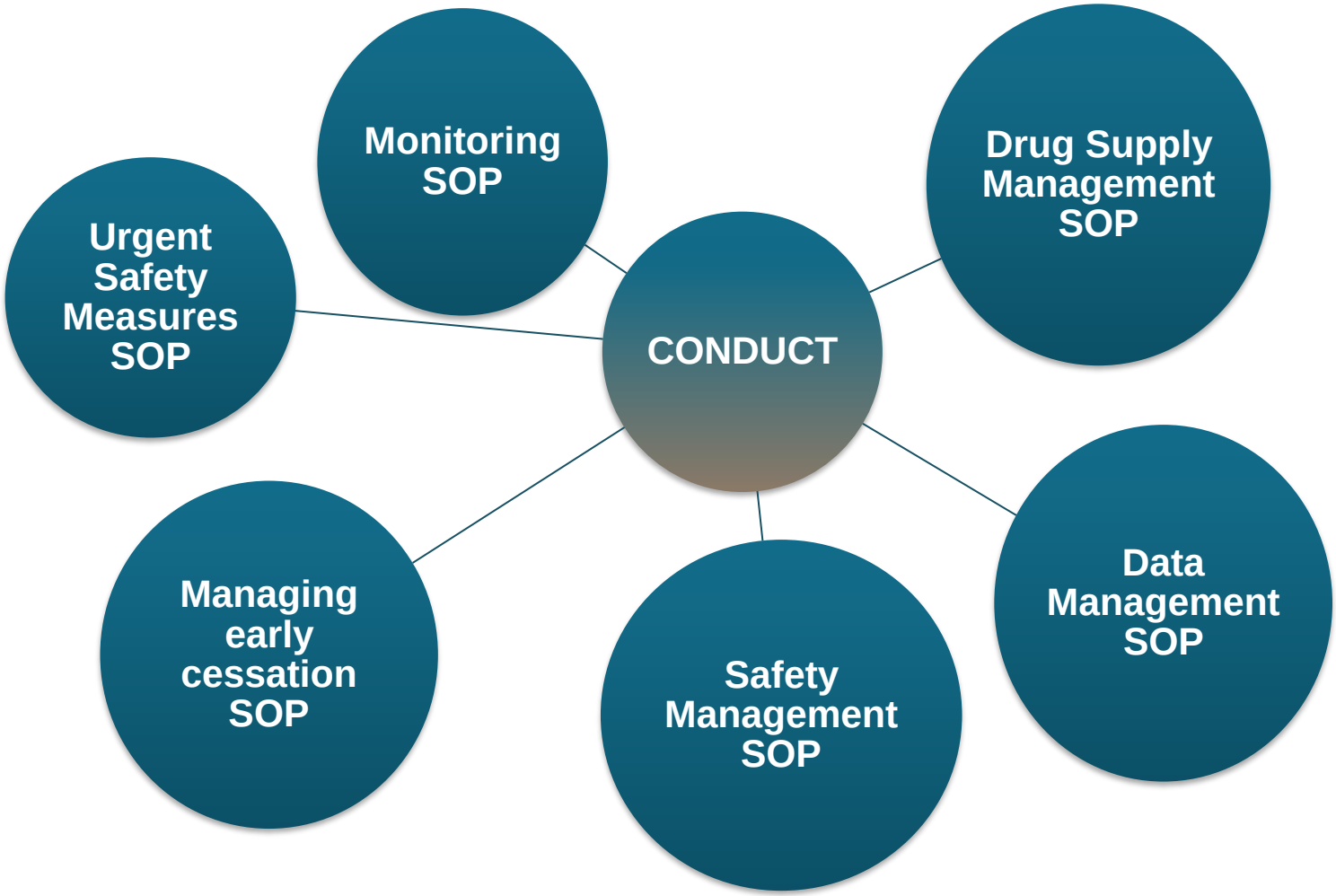
Trial Documentation

- Trial Master File (TMF)
  - **Sponsor responsibility** but can be delegated
  - Details the procedure for setting up and maintaining a TMF in **compliance with the principles of GCP** and relevant local and international regulations.
  - **Identifies the documents** that form the TMF and at what stage of the clinical trial they are required.

TMF Index Template

File #	Documents	Description *Amend this section to list the documentation present in your files*	Trial Master File	Investigator Site File	ICH GCP (reference only)	Comments *Note any concerns about the listed documentation and highlight known issues. Also note where documentation is stored if not in TMF, e.g. trial drive on network, particularly as key relevant documents will need to be printed prior to archiving.*
1	**Study Protocol/ Key documents**					
1.1	Signed protocol	Current approved version	X	X	*8.2.2* *8.3.2*	*For clarity, add a summary of the versions with approval dates in each country if there have been many protocol versions. Also add implementation dates for sites to version control summary.* *See Signing Off Formal Documents SOP*
1.2	Signed protocol – previous versions	Superseded approved versions (if applicable)	X	X	*8.2.2* *8.3.2*	*All superseded versions should be kept in the TMF.* *All locally approved superseded protocols should be kept in the relevant Investigator Site Files (ISFs).* *Key drafts and major comments should be kept in separate working files. File note, or indicate in index, their location.*
1.3.1	Sample case report forms	Current versions	X	X	*8.2.2* *8.3.2*	*For clarity, add a summary of the versions if there have been many changes. Also add implementation dates for sites to version control summary.*

Conduct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CONDUCT
Managing early cessation SOP
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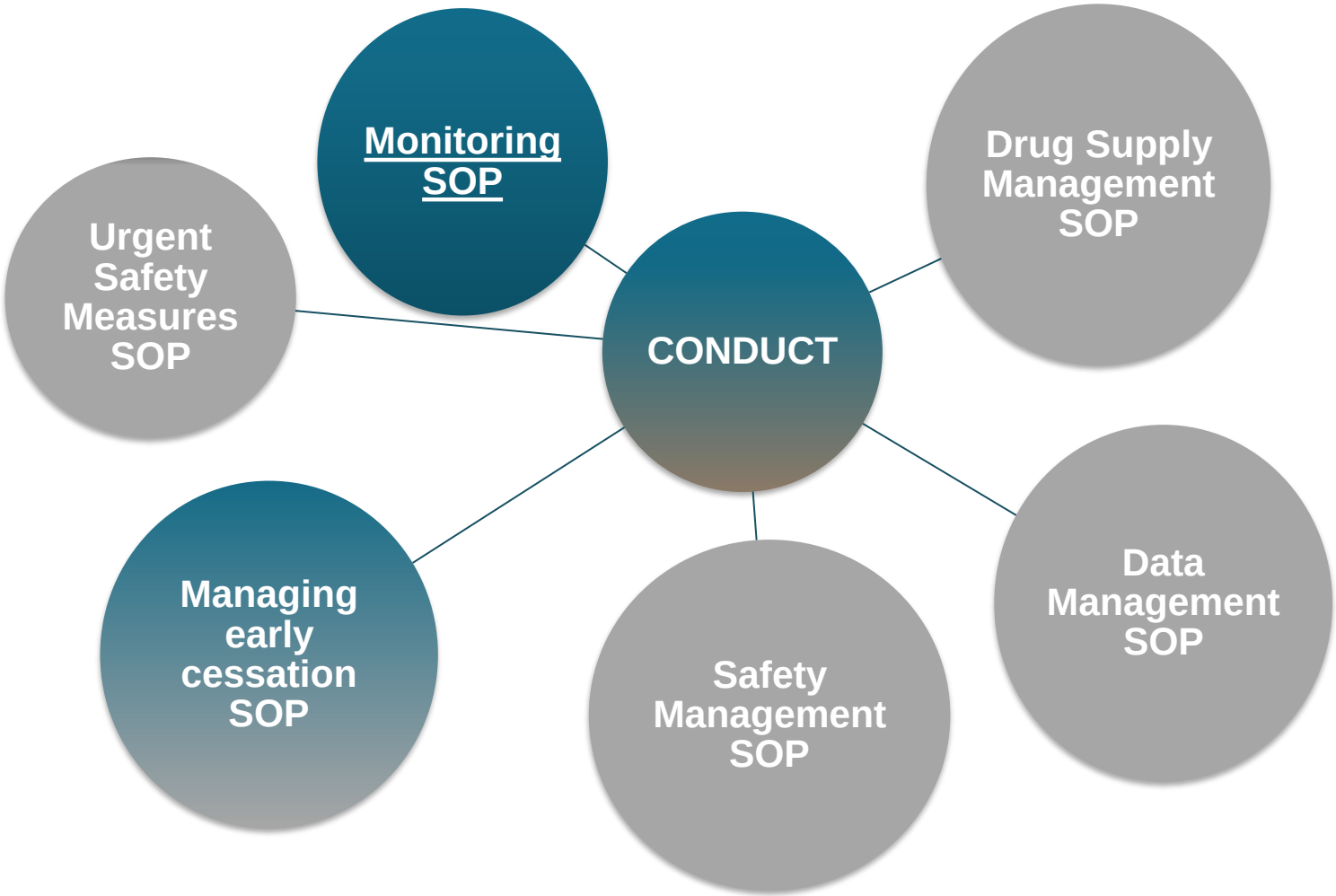
Data Management SOP

Conduct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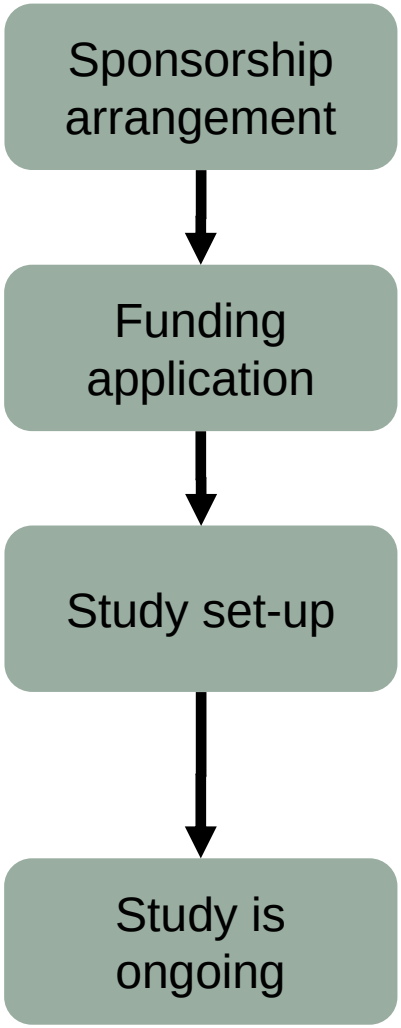
Monitoring Strategy Lifecycle



- High level risk assessment form completed
- Consider high level monitoring needs

- Consider monitoring needs and request appropriate funding

- Study risk assessment completed – identifies what requires oversight
- Monitoring Strategy devised

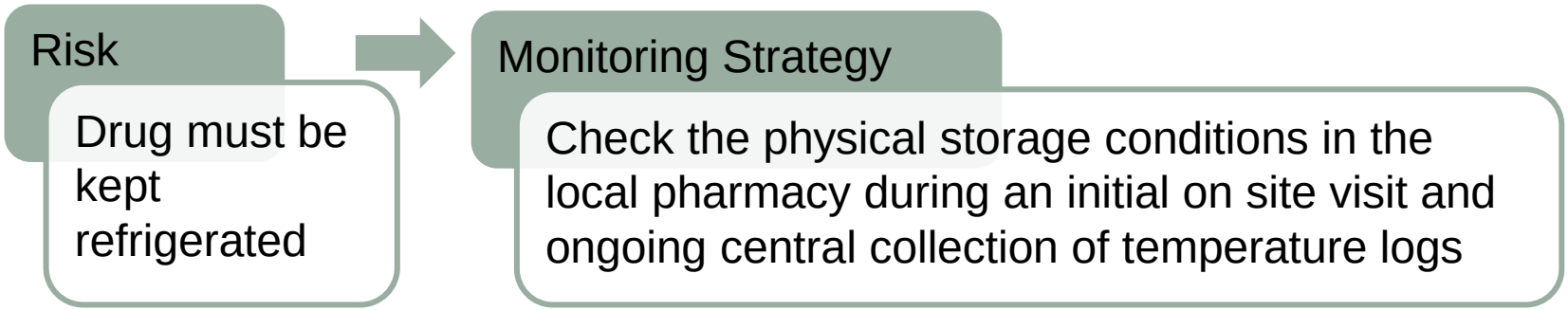
- Risk assessment is reviewed regularly
- Monitoring Strategy should be adapted accordingly

Monitoring SOP

- Outlines the minimum standards for adequate monitoring of trials and studies managed by MRC CTU.
- Details how trial and study teams should create project-specific monitoring processes based on project-specific risks, and where these monitoring processes should be documented.
- Defines the MRC CTU roles and responsibilities involved in monitoring adherence to the study protocol, the principles of GCP and the applicable regulatory requirements.

Monitoring Plan

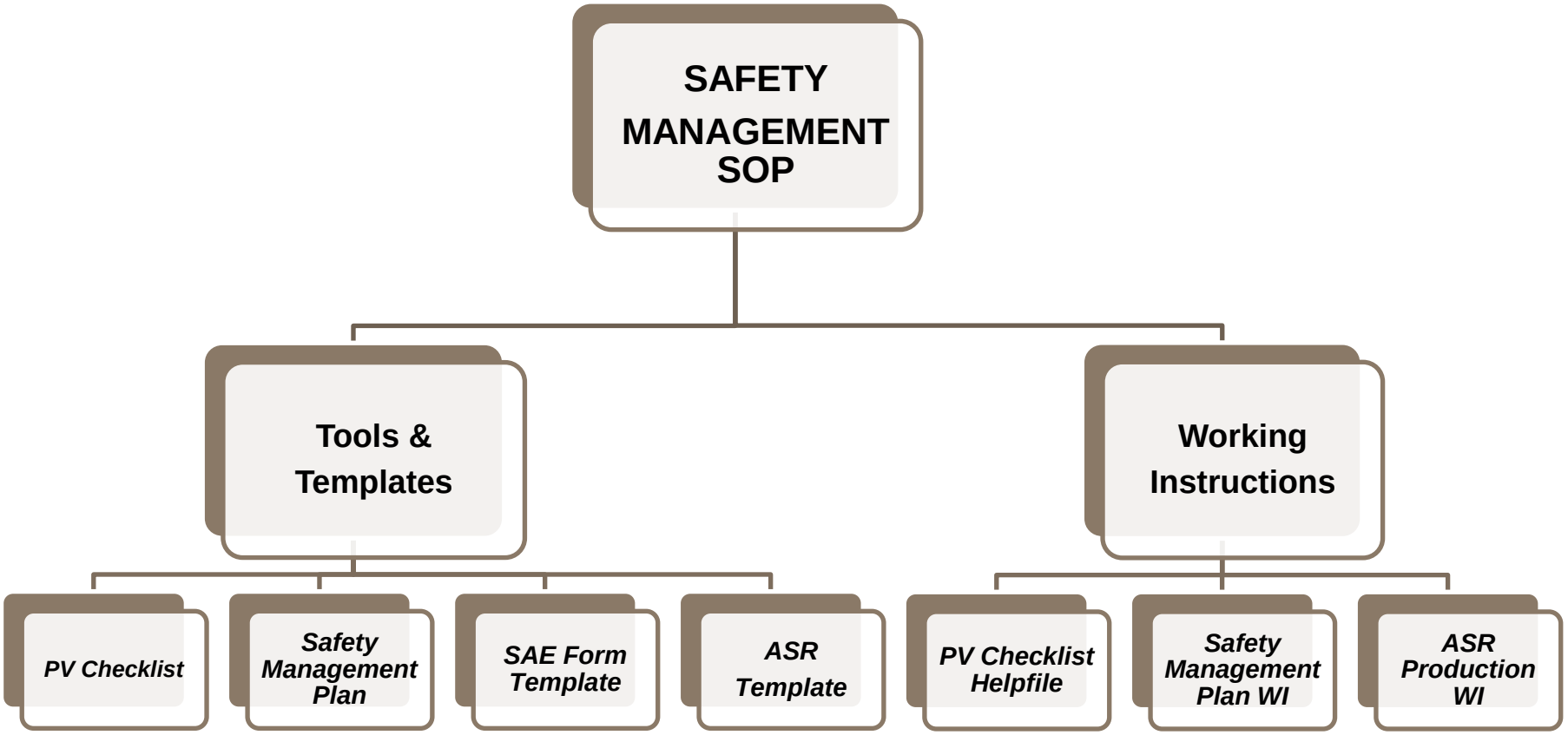
- Monitoring Plan
  - includes appropriate and specific mitigation strategies to manage the risks identified in the risk assessment



Safety Management

- Needs to be considered during design, set-up and conduct stages.
- GCP states the Sponsor is responsible for the on-going safety evaluation of the IMP
- Ensures appropriate recording and reporting of adverse events in order to ensure the continuing safety of study participants.

Safety Management SOP



Pharmacovigilance (PV) Checklist

- Following identification of risks, each trial will complete a trial specific PV Checklist in which each aspect of safety management will be considered and responsibilities will be assigned.
  - Clinical review of SAEs
  - Medical coding
  - Reference safety information
  - Pregnancy risks

Safety Management Plan

- Describe the specific safety management and related activities in the trial.
- Updated throughout the life of the trial to reflect any changes in safety management procedures.
- Contains detailed working practices related to each aspect of safety management, which are adequate for everyday use.
- Used in conjunction with the trial protocol and PV checklist

SAE Form Template

- Ensures all information required for regulatory reporting is collected
  - Seriousness criteria
  - Causality assessment
  - Expectedness assessment
- Standard template is helpful for database development

Summary

- SOPs ensure research conducted following national regulations, GCP and institutional policies.
  - help reduce errors or variations
  - allow operation efficiency
- SOPs should be supplemented with tools and templates to ensure adherence