Please see below for a link to the webinar recording for the Trials Methodology Research Partnership:

Wishing you a lightbulb moment in clinical trial monitoring

Sharon Love (University College London)

05 May 2021

On behalf of the UKCRC Registered CTU Network

The slides are also available below.

For any queries, please contact uktmn@nottingham.ac.uk

https://www.youtube.com/watch?v=fzz7LsZ1y9A

MRC Clinical Trials Unit

Smarter Studies
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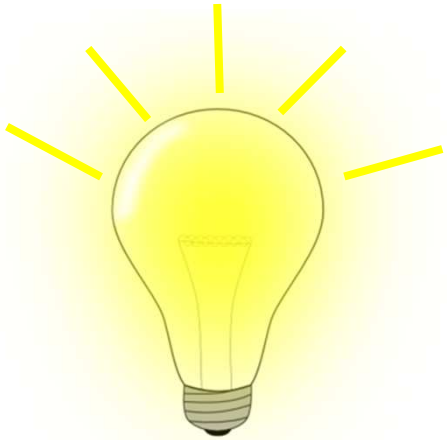
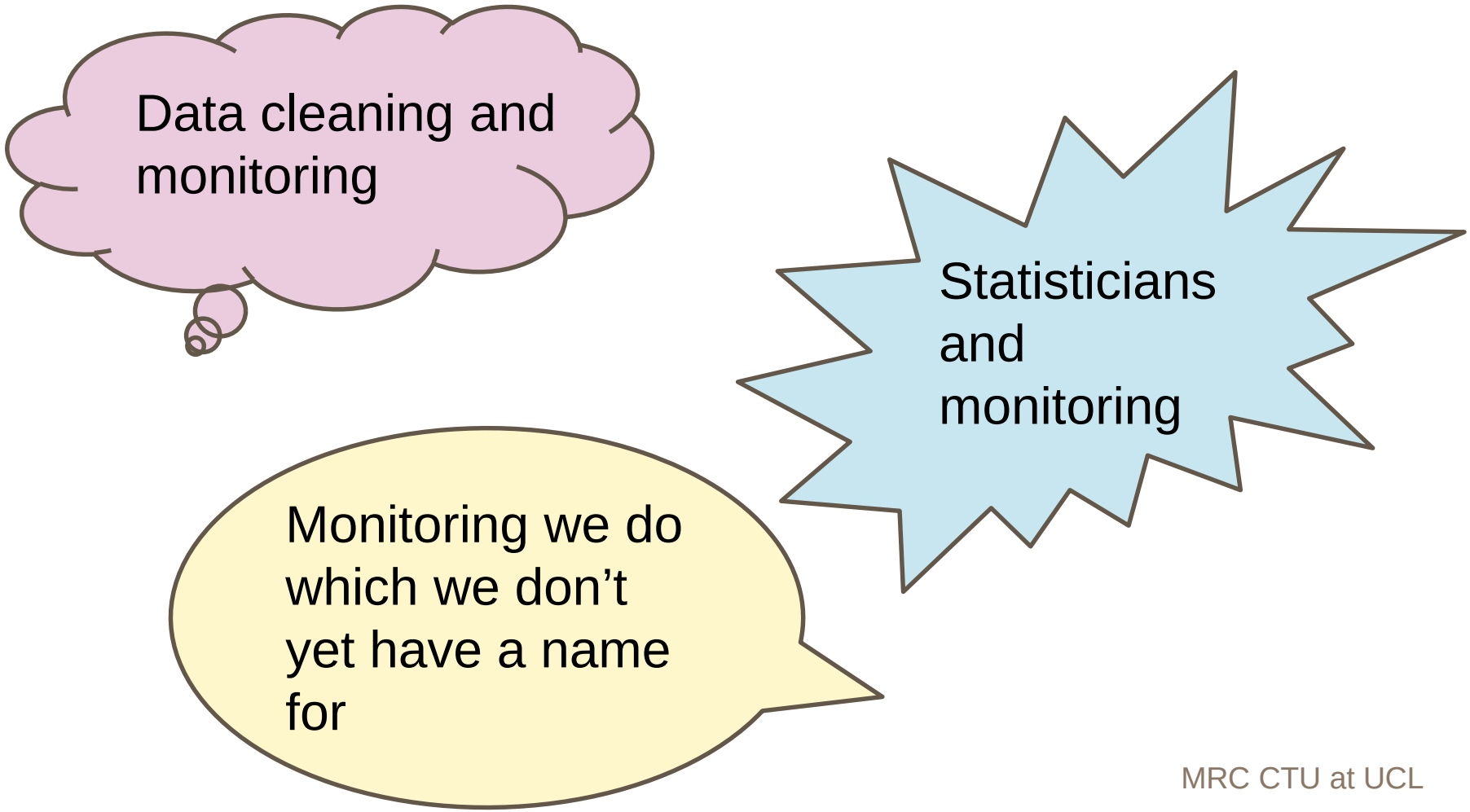
Wishing you a lightbulb moment in clinical trial monitoring

Sharon Love

5th May 2021




Data cleaning and monitoring
Statisticians and monitoring
Monitoring we do which we don’t yet have a name for


Data cleaning and monitoring

Background

SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)

Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

https://www.spirit-statement.org/

Background


CLINICAL TRIALS

Making a distinction between data cleaning and central monitoring in clinical trials

Recent examples from protocol papers to fulfil that SPIRIT criteria

“Clinical researchers, data administrators, and statistical analysts should audit the established database by the end of the study.”

“Two data managers will independently input and proofread the data. Specialists will check the data for each center every month. Relevant researchers will need to verify and correct any problems found within 1 week.”

“The study sponsor will assign an independent study auditor who will review source study documents and reports annually.”

“During the clinical study, clinical inspectors will conduct regular on-site monitoring visits to ensure that all content of the research protocol is strictly observed, and the original data are checked to ensure consistency with the CRF.”

MRC CTU at UCL

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MRC CTU at UCL

Data cleaning

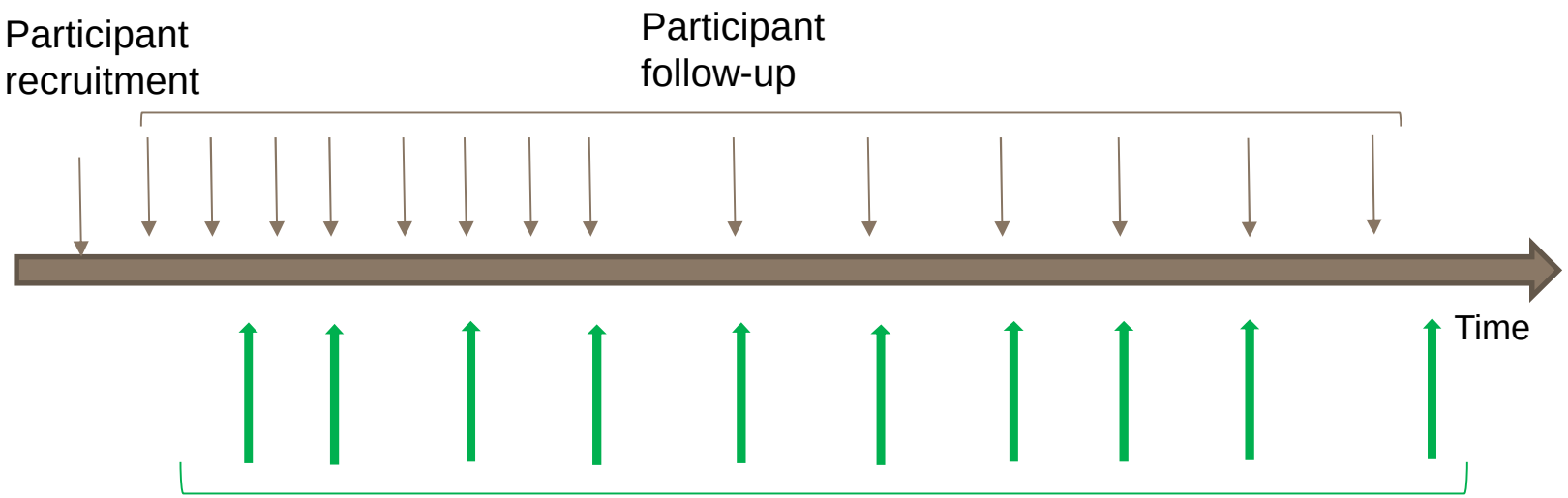
- Data cleaning addresses problems with data such as incomplete, invalid or inconsistent data.
- When data are entered, most databases have some automated checking of data and flagging of problems.
- On a regular basis or maybe before data monitoring committee (DMC) meetings, central trial team members run checks on the participant data and query any strange or required values with sites.
- Before any interim or final analysis these processes will be repeated.

These are all data cleaning activities. They happen often in the course of a trial. The main action is sending out data clarification requests.

Central Monitoring

- Central monitoring is looking to centrally identify any issues with trial conduct such as inadequate processes or procedures not being followed through a lack of clarity in the protocol or active fraud.
- Central monitoring results are an indicator of the quality of a trial and shows due diligence. Any issues found during central monitoring should be followed up by contacting the site, and may also result in actions such as the delivery of (re)training or the making of an on-site visit.
- Central monitoring need only be repeated periodically, the period depending on trial parameters such as the duration of treatment and recruitment rate and on the assessment of risk.

Example of central monitoring timepoints



Central monitoring timepoints

Similarities and differences

	Data Cleaning	Central Monitoring
Purpose	To ensure the data are accurate and complete	To ensure the trial is being run according to the protocol
Scope	Individual questions and participants	Site level, or across sites and trials
Evaluates	Issues with data recording or data entry	Issues with processes
Likely actions	Send out a data clarification request	All or any of Contact with site, Site (re-)training, On-site visit
Mutual benefit	Good data cleaning leads to fewer monitoring actions	Can include consideration of the success of data cleaning e.g. using a metric of the percentage of data queries outstanding at 2 months

Similarities and differences

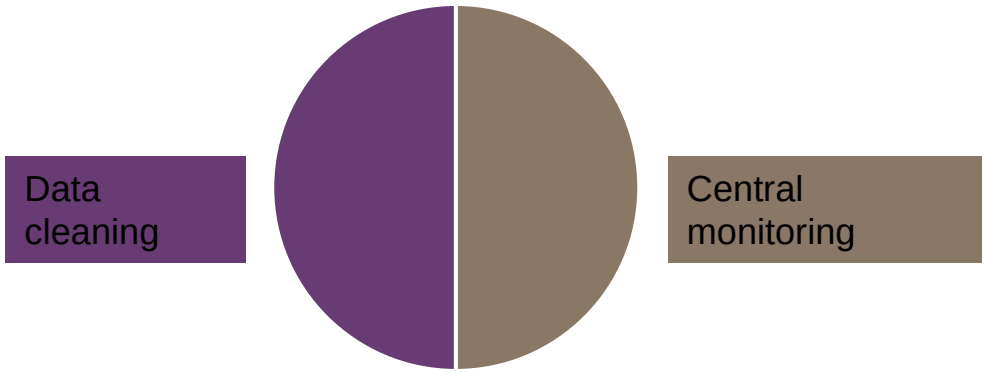
	Data Cleaning	Central Monitoring
Frequency	Soon after data entry	Periodic, depending on the risk
DMC and analyses	Cleaning activities may be increased before each interim and final analysis	Periodically performed but may be also carried out before each DMC review and analysis
Specification	In data management plan	In trial monitoring plan
Summary measure of effectiveness	Often counts or percentages e.g. of non-missing variables or case report forms or variables out of range	Can be summarised as “quality tolerance indicators” to give a single value or small number of values to express the current quality of the trial
Funding	Often bundled in with trial staff time	Sometimes encompassing dedicated staff (monitors)

Why it matters

- Data cleaning and monitoring can occur at the wrong times with respect to each other
- Monitoring can happen too often
- Resources are required for each of data cleaning and central monitoring
- Thinking of them as one encourages one to not be done well enough
- Risks must be mitigated
- Data cleaning is done on individual patient data and central monitoring is done at site level
- It is difficult to communicate trial results if we are using different meanings
- It is difficult to do and communicate the results of monitoring research if we do not have a common understanding

Summing up data cleaning and monitoring

- Data cleaning and central monitoring are practically and conceptually different
- Data cleaning and central monitoring need to be correctly defined and used in order to
  - Communicate the adequate conduct of the trial
  - To ensure adequate risk mitigation
  - To ensure the data and trial integrity



Reference - DOI:10.1177/1740774520976617

Data Management and Trial Conduct

CLINICAL TRIALS

Making a distinction between data cleaning and central monitoring in clinical trials

Sharon B Love, Victoria Yorke-Edwards, Carlos Diaz-Montana, Macey L Murray, Lindsey Masters, Michelle Gabriel, Nicola Joffe, Matthew R Sydes

"Data cleaning" and "central monitoring" have become intertwined to the potential detriment of trial conduct. They are practically and conceptually different. What is data cleaning, what is central monitoring and why does the difference matter?

Early clinical trials collected data on punch cards and then on paper. As computers became


Statisticians
and
monitoring

Why we do monitoring - ICH GCP E6(R2)

5.18.1 Purpose

- *The purposes of trial monitoring are to verify that:*
- *(a) The rights and well-being of human subjects are protected.*
- *(b) The reported trial data are accurate, complete, and verifiable from source documents.*
- *(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).*

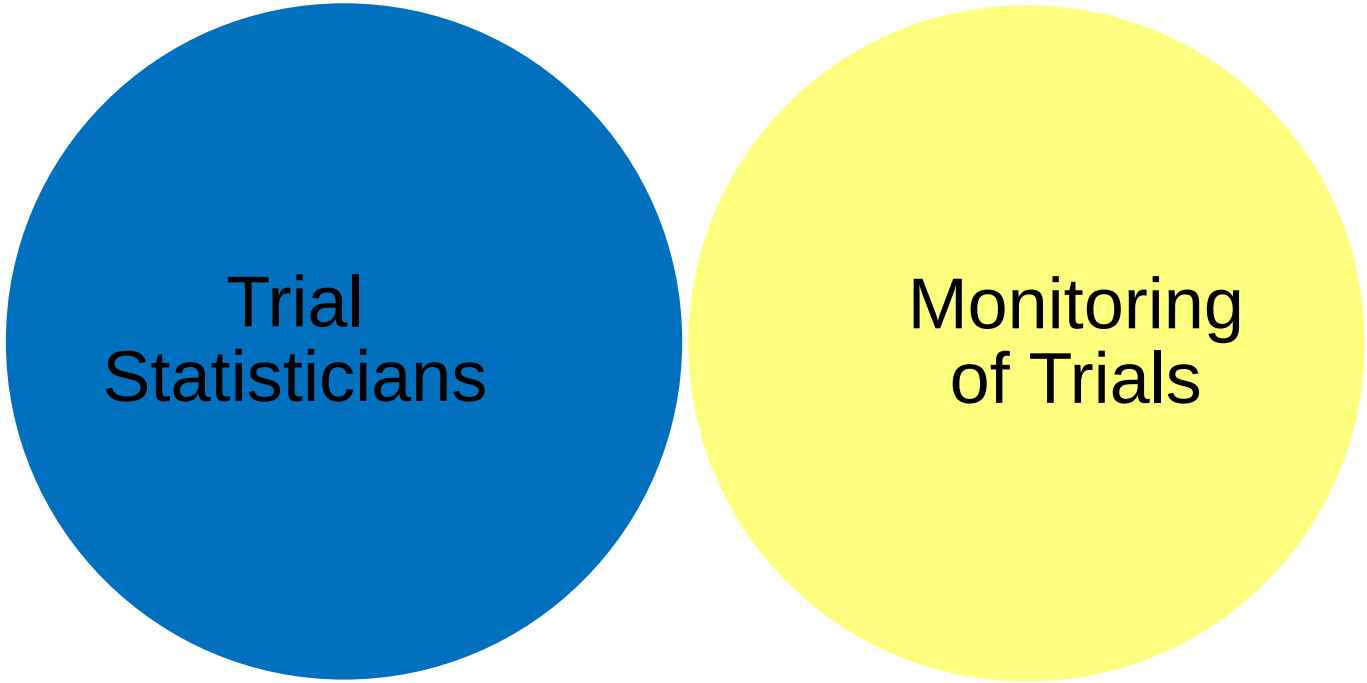
Site	Recruited	Total Outstanding (O/S)	% of site's CRFs that are O/S	O/S >6 mths	% data return	% of total O/S
	16	5	2.1%		97.9%	0.4%
	55	67	6.3%	16	93.7%	5.8%
	24	6	1.2%	2	98.8%	0.5%
	10	3	1.8%		98.2%	0.3%
	52	84	9.7%	61	90.3%	7.2%
	6	9	7.2%	4	92.8%	0.8%
	59	11	1.0%	1	99.0%	0.9%
	20		0.0%		100.0%	0.0%
	69	8	0.5%	8	99.5%	0.7%
	22	86	22.3%	52	77.7%	7.4%
	24	2	0.4%		99.6%	0.2%
	3		0.0%		100.0%	0.0%
	25	18	4.4%	5	95.6%	1.5%
	13	3	1.2%	1	98.8%	0.3%
	1		0.0%		100.0%	0.0%

Hospitals with more than 10 patients and either less than a 90% data return rate or more than 5% of the total trial data outstanding have been highlighted.

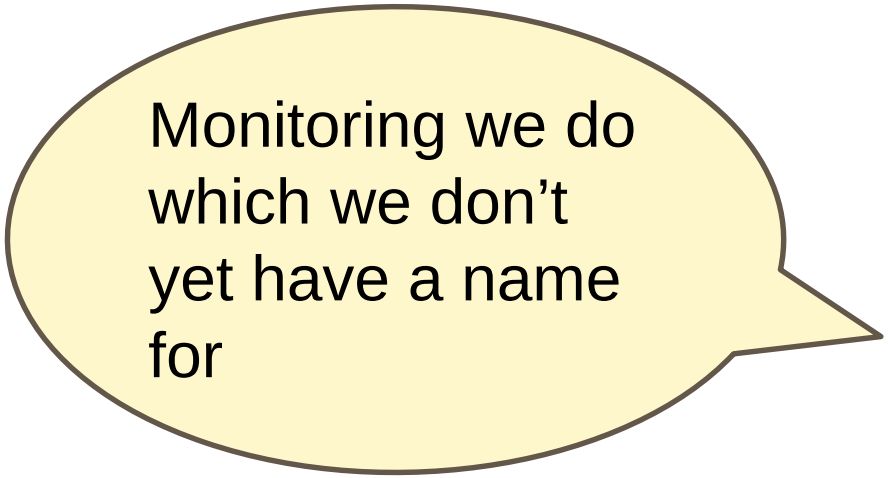
Site	Number of patients randomised	Number of SAE	count per 100 patients
Leicester Royal Infirmary, Leicester	252	77	30.6
Leicester General Hospital, Leicester	133	64	48.1
Queen Alexandra Hospital, Portsmouth	108	19	17.6
Torbay Hospital, Torquay	65	26	40.0
Craigavon Area Hospital, Craigavon	50	16	32.0
Countess of Chester Hospital, Chester	48	11	22.9
Royal Derby Hospital, Derby	35	27	77.1
North Tyneside General Hospital, North Shields	34	10	29.4
Royal Liverpool Hospital, Liverpool	34	13	38.2
Royal Cornwall Hospital, Truro	33	5	15.2
Mater Infirmorium Hospital, Belfast	32	6	18.8
Cumberland Infirmary, Carlisle	31	2	6.5
Victoria Hospital Kirkcaldy	28	8	28.6
Lagan Valley Hospital, Lisburn	28	8	28.6
North Manchester General Hospital, Manchester	21	1	4.8
Stepping Hill Hospital, Stockport	21	8	38.1
TOTAL			30.3

Site	Number of patients randomised	Number of withdrawals from treatment	count per 100 patients
Leicester Royal Infirmary, Leicester	252	60	24
Gloucestershire Royal Hospital, Gloucester	243	79	33
Leicester General Hospital, Leicester	133	24	18
Queens Medical Centre, Nottingham	53	13	25
Ninewells Hospital, Dundee	51	7	14
Royal Liverpool Hospital, Liverpool	34	5	15
Royal Cornwall Hospital, Truro	33	7	21
Victoria Hospital Kirkcaldy	28	5	18
Harrogate District Hospital	27	2	7
Altnagelvin Hospital, Londonderry	27	4	15
Yeovil Hospital, Yeovil	26	1	4
Blackpool Victoria Hospital, Blackpool	26	4	15
Alexandra Hospital, Redditch	24	7	29
Sandwell General Hospital, Lyndon	24	2	8
North Manchester General Hospital, Manchester	21	2	10
Stepping Hill Hospital, Stockport	21	10	48
TOTAL			21

Statisticians and Monitoring



Statisticians and Monitoring


Monitoring we do
which we don’t
yet have a name
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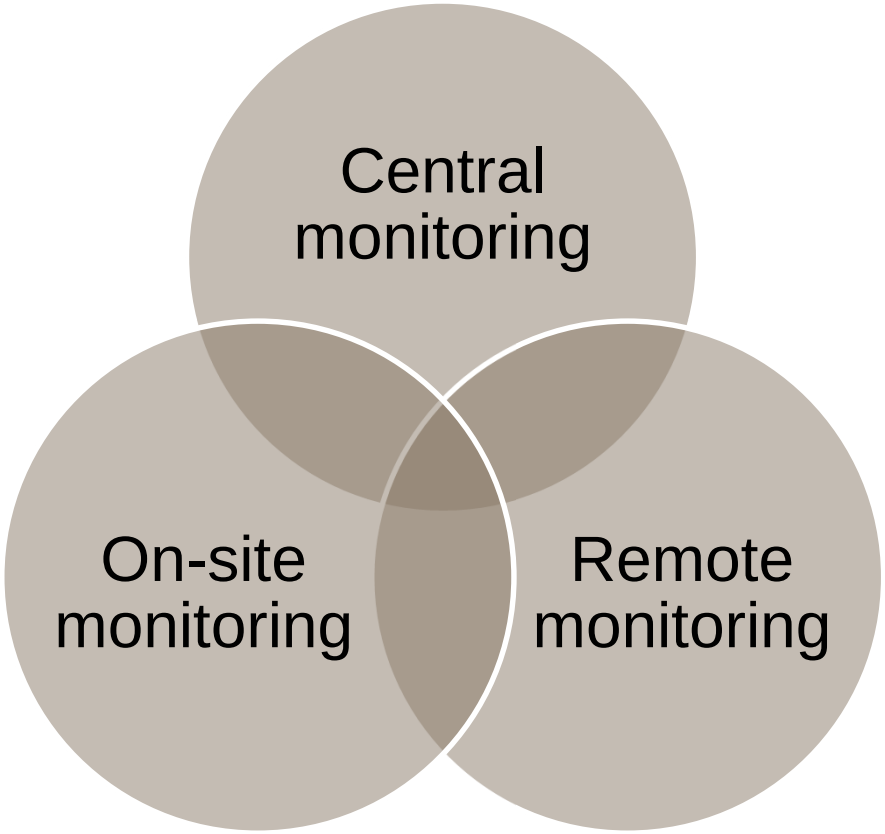
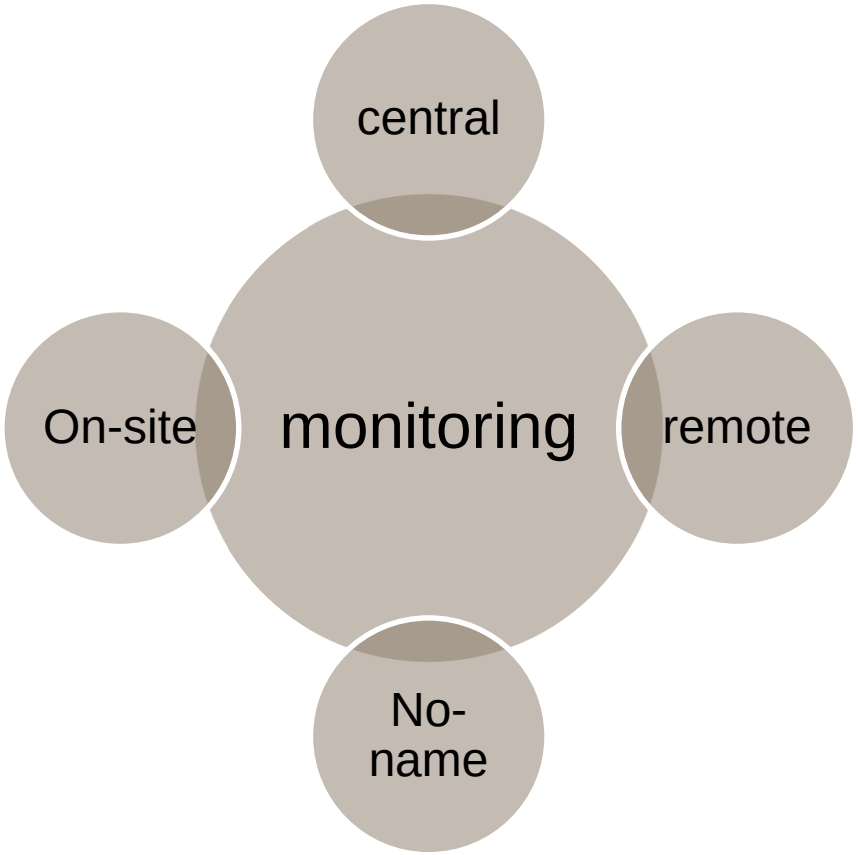
Definition of central monitoring

Central monitoring is looking to centrally identify any issues with trial conduct such as inadequate processes or procedures not being followed through a lack of clarity in the protocol or active fraud.

How to you classify this task?

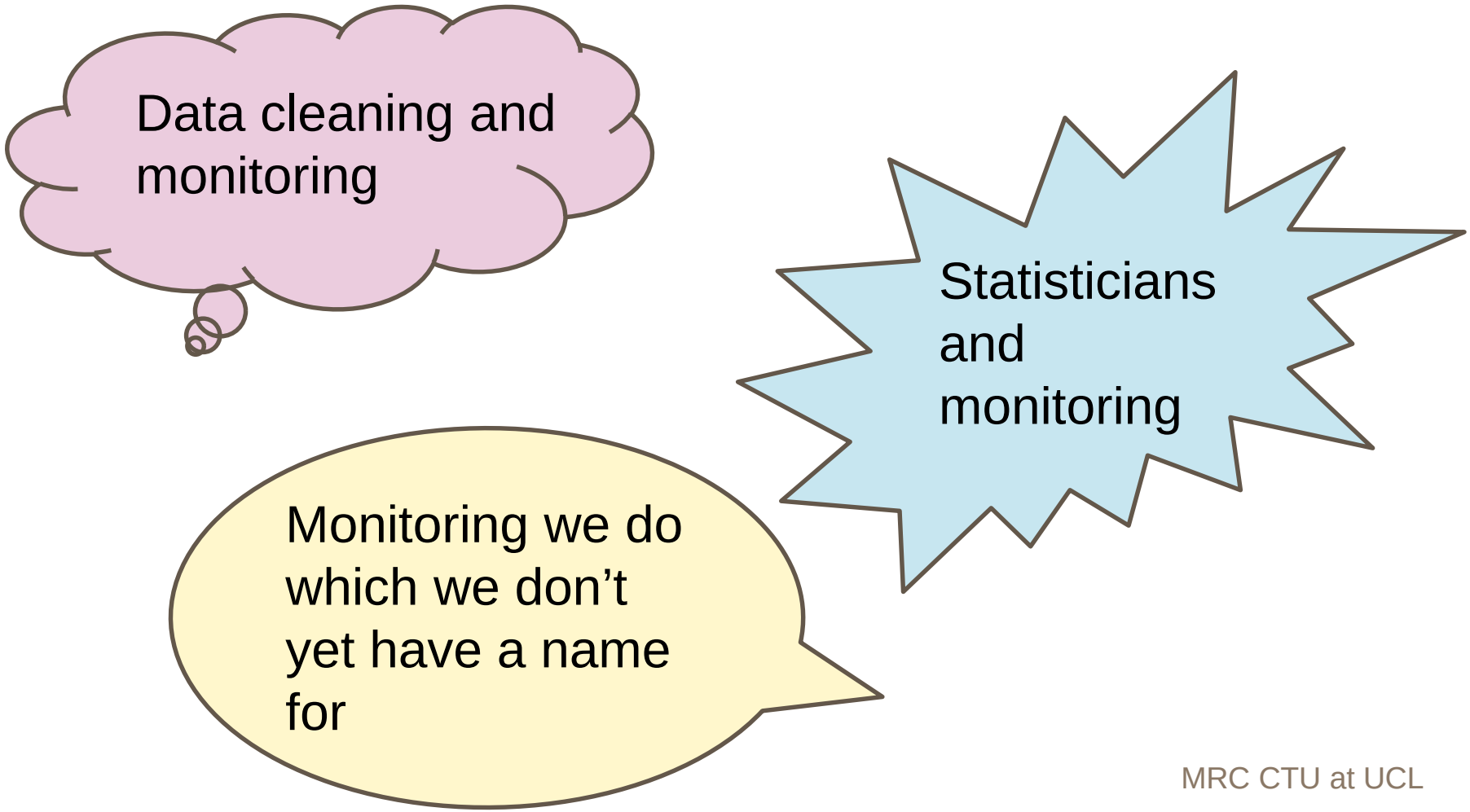
- Do you collect delegation logs every 6 months and check that the CRF have been correctly signed?
- What do you call this? Who does it


Central monitoring
On-site monitoring
Remote monitoring


central
On-site
monitoring
remote
No-
name

Why does it matter?

- If work is not labelled as monitoring, when looking at the monitoring of a trial you do not find it
- Difficult to share experience
- Research is unlikely to happen
- Communication is impossible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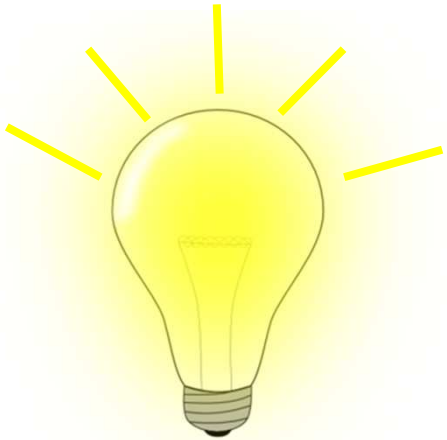
Summary

We need to clarify data cleaning and monitoring

We need to get all the people who do monitoring together working as one

We need to develop terminology where needed



Current UKCRC, TMRP and MRC CTU projects

Project	Project lead	Date first output due
Risk Assessment Template	UKCRC Task & Finish Monitoring Group	Dec 2021
Metrics and thresholds		Dec 2021
Training handbook and half day course		Jun 2021
Purposes of monitoring	TMRP Trial Conduct Working Group Data Quality and Monitoring Group (DQM)	Sep 2021
How to measure if you monitoring is good enough		Dec 2023
What purpose do our actions fulfil		Dec 2023
How metrics vary across time	MRC Clinical Trials Unit at UCL	Jun 2021
Data monitoring plan template		Dec 2023
Storage of monitoring action		Sep 2022
Monitoring change during the pandemic		Sep2021

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UKCRC Registered CTU Network

Monitoring Task and Finish Group National Meeting

9 & 16 June 2021, 10:00 – 12:30

Via Microsoft Teams

To Join: Please contact your monitoring representative in your CTU who has been sent joining details

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THANK YOU

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