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

GCP but not as you know it – developing Good Statistical Practice training

Deborah Stocken (University of Leeds)

09 June 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=anzpJiGmbfE

UKCRC CTU Statisticians Operational Group

UKCRC Registered Clinical Trials Units

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GCP but not as you know it….

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Professor of Clinical Trials Research and Head of Statistics

Clinical Trials Research Unit, University of Leeds

FUNDED BY NIHR | National Institute for Health Research

GCP but not as you know it….

- GCP: Good Clinical Practice
- GSP: Good Statistical Practice
- *GCP for Statisticians*

Why GCP?

- GCP: Good Clinical Practice
- International ethical and scientific guidelines and quality standards
  - Rights and wellbeing of participants are protected
- Scientific integrity of trial
  - design, data collection and reporting
  - Unbiased allocation, treatment, outcome assessment

ICH Definition

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"Good clinical practice is a set of internationally recognised ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects."

"Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible." ICH GCP Guideline

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ICH GCP

- 13 principles stated ICH Harmonised Tripartite Guideline for GCP 1996, updated 2016
  - a unified standard for EU, US and WHO
  - intended for clinical trial submissions to regulatory authorities
  - principles applicable to other clinical investigations

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE (ICH)

ICH HARMONISED GUIDELINE

INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE ICH

E6(R2)

ICH Consensus Guideline

UK Regulations

STATUTORY INSTRUMENTS

2004 No. 1031

MEDICINES

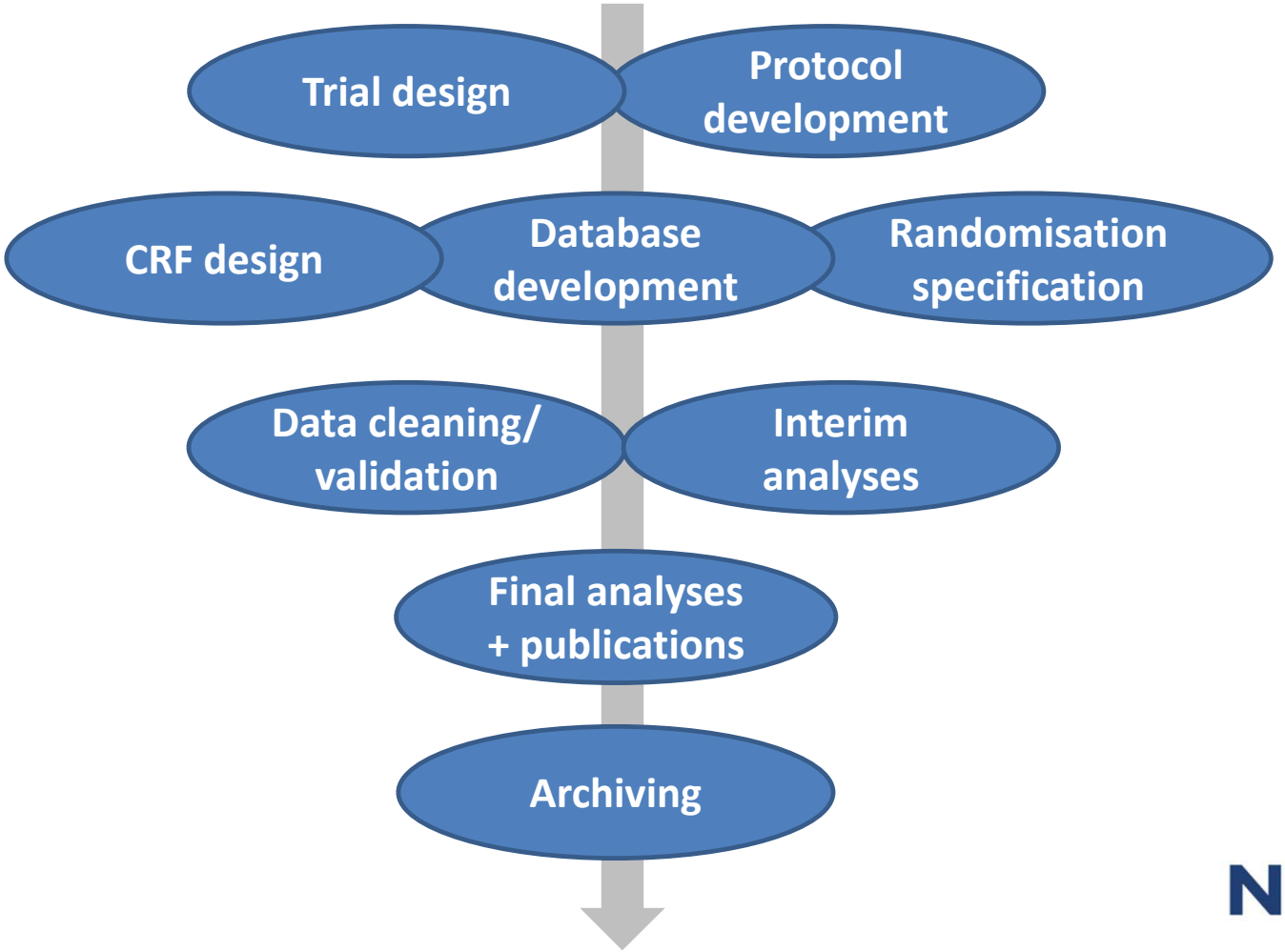
The Medicines for Human Use (Clinical Trials) Regulations 2004

- GCP is a legal requirement for CTIMPs
  - Inspected metric
- Principles applicable to all clinical trials research

Delegated Duties

- **Sponsor is the legal organisation with trial responsibility**
  - initiation, management, monitoring, insurance
- Sponsor can delegate duties but not responsibility
  - this **must** be clearly evidenced
- Statistical activities are delegated duties
  - ICH acknowledge the role of the Statistician as essential

Statistical Activities in clinical trials



Documentation

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Essential Role

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"Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his or her respective tasks(s)" ICH-E6

European Medicines Agency

September 1998
CPMP/ICH/363/96

ICH Topic E 9
Statistical Principles for Clinical Trials

"it is assumed that the actual responsibility for all statistical work associated with clinical trials will lie with an appropriately qualified and experienced statistician" ICH-E9

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WHO

Special Communication JAMA November 27, 2013 Volume 310, Number 20

World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

World Medical Association

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

GCP Training

- *"the trial statistician should have a combination of education/training and experience sufficient to implement the principles articulated in this guidance."* *ICH-E9*
- GCP impacts on statistics in terms of **processes** being followed
  - methodological aspects are covered by peer review
- Statistical processes not explicitly covered by existing training
  - does not include guidelines for statistical conduct
- GCP training can be tailored to the individuals roles and responsibilities HRA, MHRA

UKCRC CTU Statisticians Scoping

- Initial scoping exercise of current GCP training
- UKCRC CTU Statisticians meeting
  - attended by at least 1 senior statistician from each of the 45 UKCRC CTUs registered at that time
- Although interesting and research related, the GCP training statisticians received was felt to be unrelated to their statistical role
- All but one person at the meeting felt there was a need for more role specific training

UKCRC CTU Statisticians Survey

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	No.Units	%
Primary role		
Senior statistician	34	76%
Statistician	11	24%
Years worked in clinical trials		
<1 year	4	9%
1-5 years	9	20%
5-10 years	10	22%
>10 years	22	49%
Predominantly working in clinical trials in:		
CTIMP	39	87%
Surgical	23	51%
Medical device	20	44%
GCP training received	44	98%
Type(s) of GCP training received*		
NIHR (face-to-face or online)	26	57%
In-house	19	43%
Institute of Clinical Research (ICR)	5	11%

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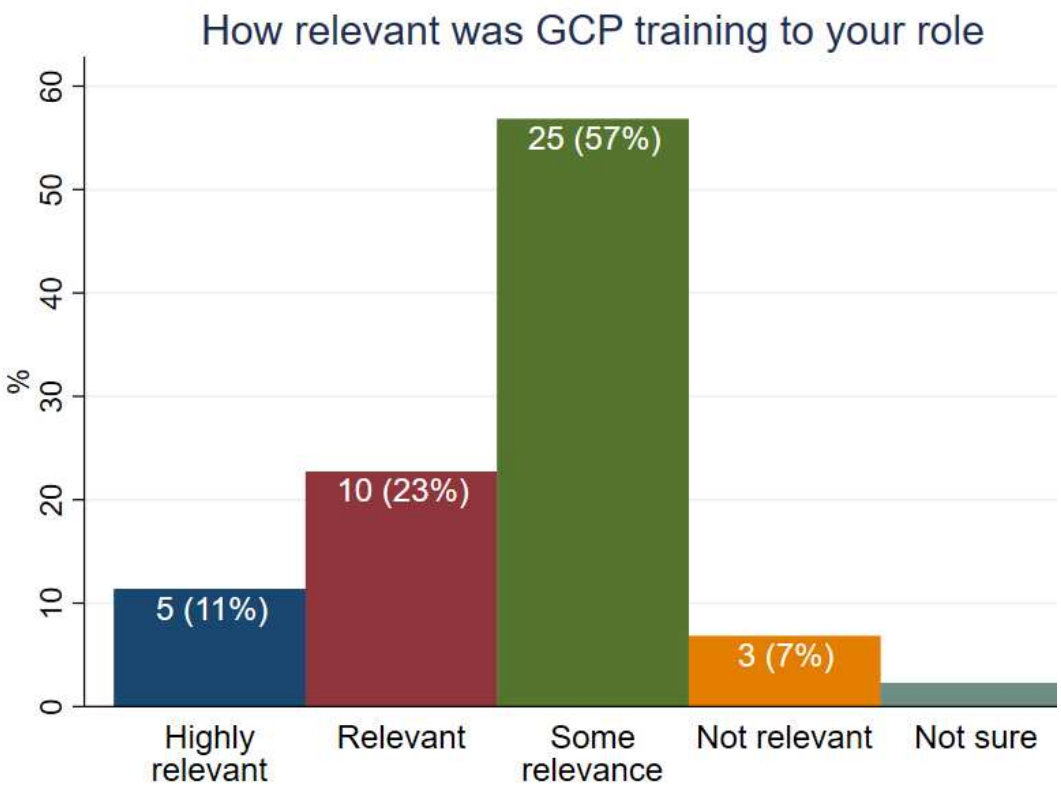
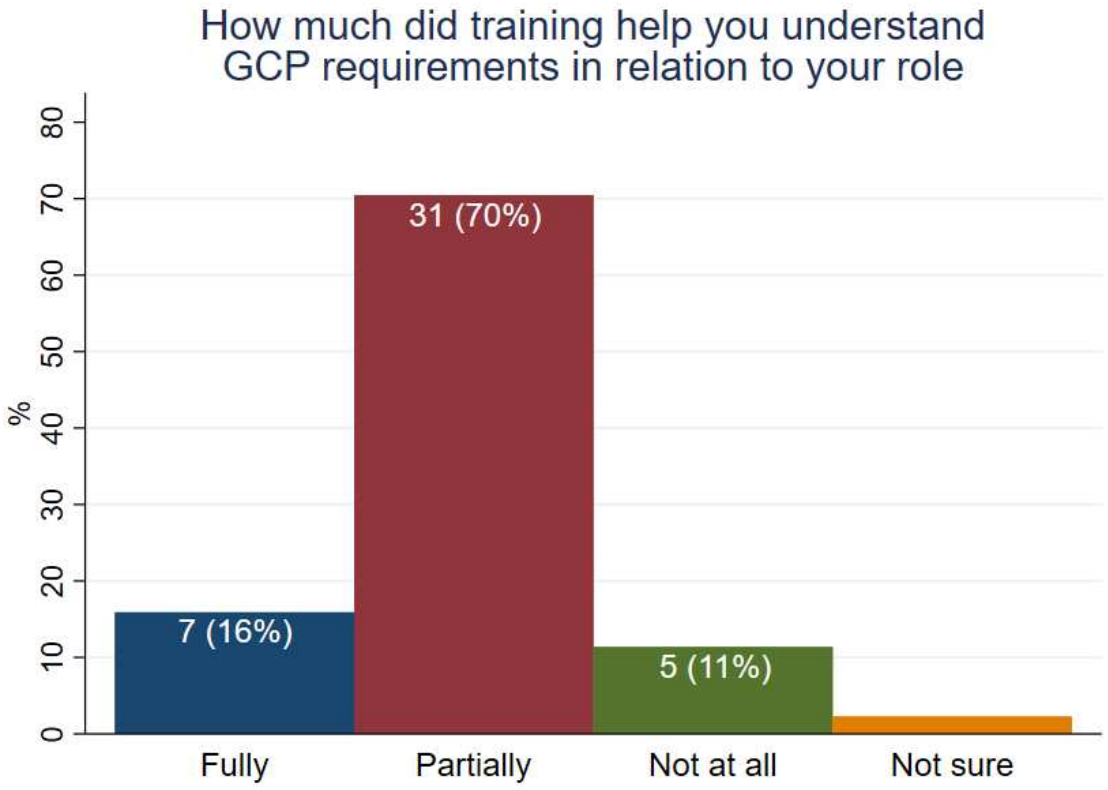
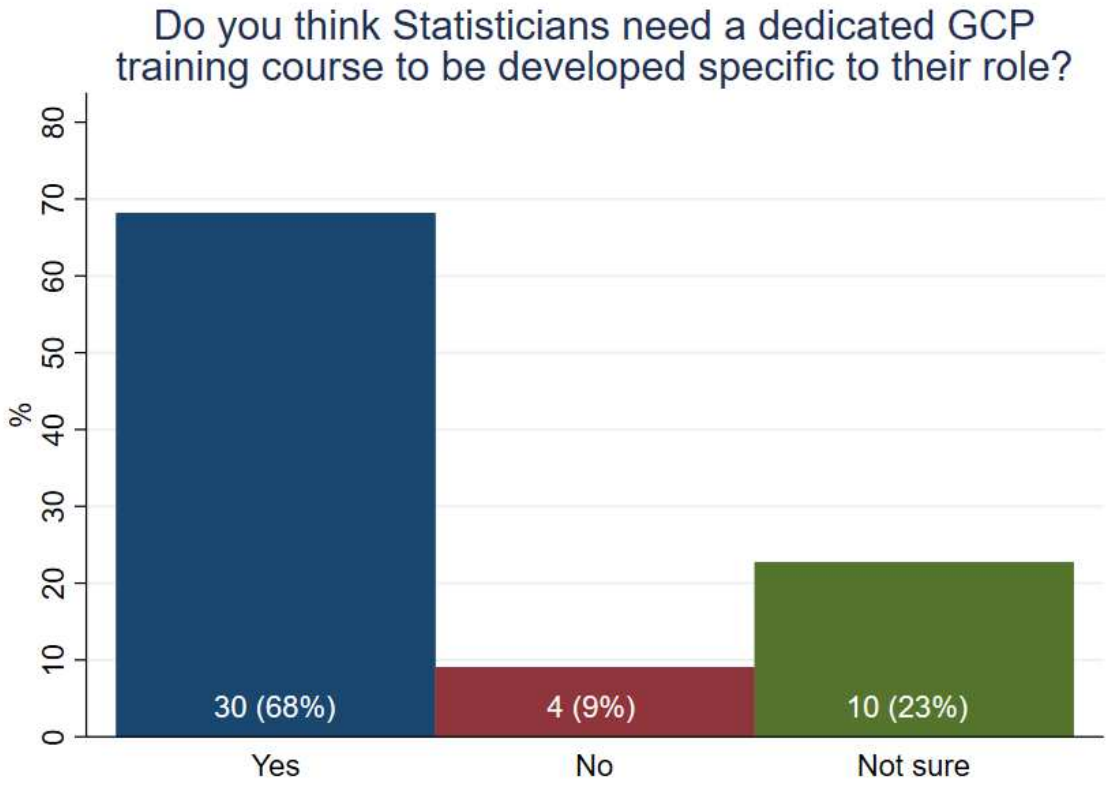
UKCRC CTU Statisticians Survey





UKCRC CTU Statisticians Survey



MHRA Inspection Findings

- Insufficient documentation of statistical processes
- Validation of analysis programming
- Inability to link output in report/publication to programming output
- Inadequate or poorly documented validation of programming for figures, tables + listings
- No “good programming practice” recommendations in place
- No control over hard coding
- Data security – protection of analysis datasets
- Unclear process for data management end and statistical analysis start

Validation of Statistical Programming V1.0. Gamble C, Kean S et al.

GSP Project

- Survey confirmed the need and clear desire for the development of a dedicated GCP training for statisticians

- The aim of the GSP project is to develop dedicated GCP training materials tailored to statisticians to equip them with the knowledge they need to better understand and implement GCP requirements in relation to their roles and responsibilities

Methods

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Methods

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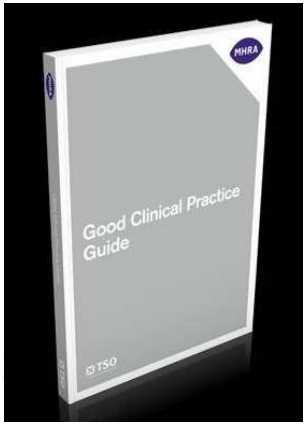
- Development of GSP training material
- Critical review and piloting 1
- Critical review and piloting 2
- Online tool development
- Input from funders + regulators
- Dissemination, maintenance
- Outputs and Launch

- Based predominantly on MHRA GCP
- Covers the role of a statistician across all relevant processes
- Distinguishes regulatory requirements from recommendations and good practice
- Includes group exercises and real-life scenarios



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Methods

- Critical Review and Piloting
- Face-to-face training
- Statistics teams at 5 UKCRC CTUs
- Extensive, detailed feedback on course content

CTU Feedback

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"something the stats community definitely needs and pleased that this is being taken forward"

"this is a really valuable tool to add to our training";

"I wish I'd had this when I first started out"

"the general feeling was that it was a lot more useful than an afternoon spent at standard GCP training"

"people were engaged… thinking if any [local] practices could be improved"

"the face-to-face aspects are particularly useful as this enabled us to discuss the various aspects in relation to our CTU SOPs, processes and documentation etc."

"all-in-all that was a very positive experience"

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Methods

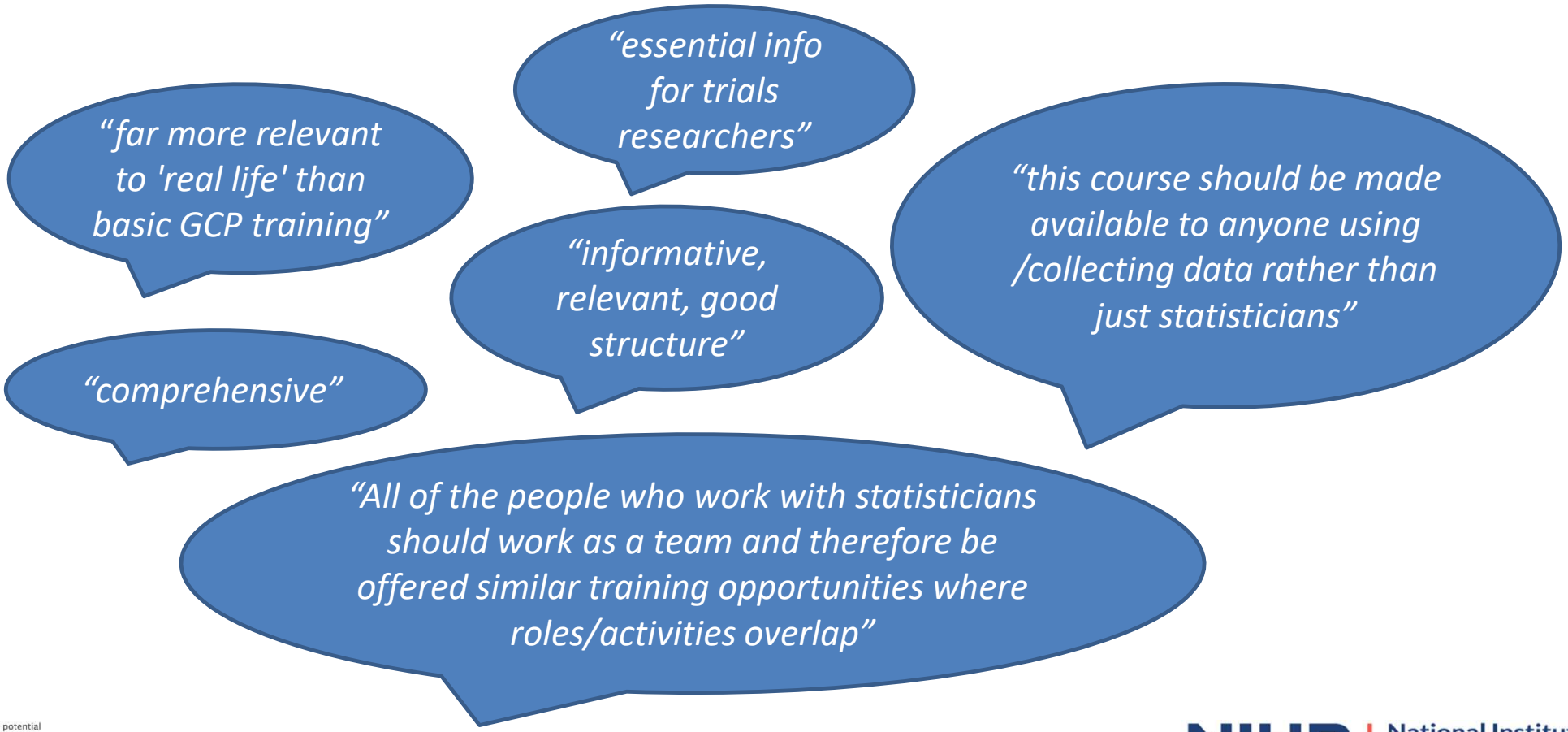
- Critical Review and Piloting
- Face-to-face training
- Delivered by course developers
- NIHR Researchers
  - NIHR Statistics Group (11 groups)
  - NIHR Researchers (14 non-CT staff)

NIHR Feedback

	NIHR Statistics Group (N=11 groups)		NIHR Unit (N=14 staff)	
The training material was relevant to my role				
Strongly agree	5	45%	8	57%
Agree	6	55%	5	36%
Neutral	0	0%	1	7%
The training material increased learning & understanding of GCP requirements in relation to my role				
Strongly agree	6	55%	7	50%
Agree	3	27%	7	50%
Neutral	1	9%	0	0%
Not answered	1	9%	0	0%
I will be able to apply new learning /skills				
Strongly agree	5	45%	3	21%
Agree	5	45%	10	71%
Neutral	1	9%	1	7%
The session was clear and well presented				
Strongly agree	5	45%	8	57%
Agree	5	45%	6	43%
Neutral	1	9%	0	0%
The session was interesting and relevant				
Strongly agree	4	36%	6	43%
Agree	6	55%	7	50%
Neutral	1	9%	1	7%

NIHR Feedback

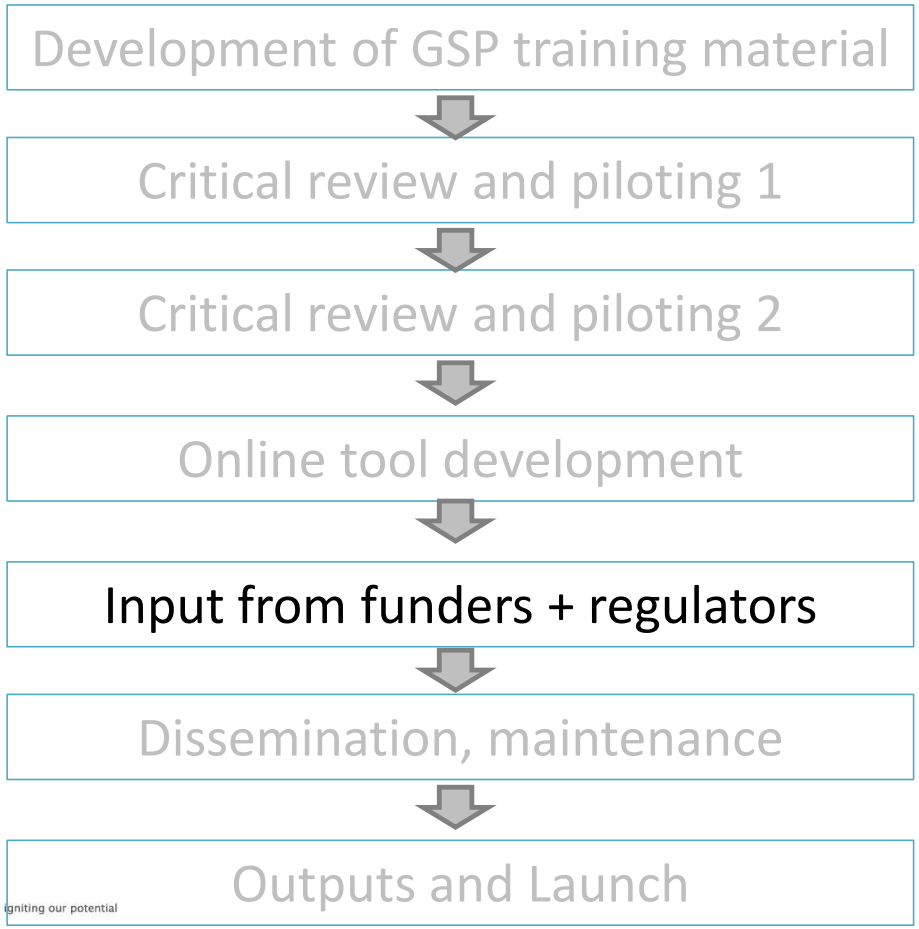
- All attended would recommend the session to a fellow researcher



Methods

- Offers flexibility and accessibility to statisticians across a range of environments and circumstances
- Content equivalent to face-to-face training
- Available through NIHR Learn portal
- Currently amending group exercises

Methods



- MHRA review of slide-set
- NIHR report under review
- Certification confirmed
  - NIHR Learn, UKCRC CTU

Methods

Materials will be freely available:

1. to CTUs via the UKCRC online platform
2. to NIHR researchers via the NIHR Learn platform
3. worldwide via email contact directly to the University of Leeds

- Conducive as pre- or post- conference training at relevant statistical and/ or clinical trials conferences

GSP Training Outline

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Module 1	Module 2	Module 3	Module 4	Module 5
Core GCP & Regulations	Record Keeping & Documentation	Trial Design	Data management	Statistical analysis & reporting

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GSP Learning Objectives

UKCRC Registered Clinical Trials Units

Module 1	Module 2	Module 3	Module 4	Module 5
Core GCP & Regulations	**Record Keeping & Documentation**	**Trial Design**	**Data management**	**Statistical analysis & reporting**
• UK regulations • ICH GCP • Roles & responsibilities • Informed consent • Pharmacovigilance • Serious breaches	• Quality systems • Training • Key trial documents • Trial Master Files • Archiving	• Trial design • Protocol development • Randomisation • Blinding	• Case Report Forms • Database build & testing • Data cleaning / validation • Central and statistical monitoring • Data coding • Database lock	• Statistical analysis plans • Analysis populations • Statistical programming • Audit trail & Quality Control • Blinding & interim data access

Areas of Direct Relevance

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Areas of direct relevance to statisticians
☐ Requirement for a statistical analysis plan (SAP) and recommendations around timing of sign-off (Module 5)
☐ Documentation of protocol non-compliances and exclusions from per-protocol populations (Module 5)
☐ Processes and documentation to be in place for formal interim analyses (Module 4)
☐ Recommendations for blinding and interim data access, e.g. for Data Monitoring Committee reports (Module 5)
☐ Security of datasets and analysis files (Module 5)
☐ Recommendations for statistical programming practices, including controls over hard-coding (Module 5)
☐ Version control of statistical reporting and output (Module 5)
☐ Requirement for an audit trail to link output used in a report or publication back to programming output (Module 5)
☐ Validation of statistical programming and quality control checks of the statistical analysis process (Module 5)
☐ Computer system validation (Module 5)
• Specification, production and control of the randomisation schedule/code (Module 3)

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Other Statistical Input

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Areas usually requiring statistical input/involvement
☐ Statistical input into trial design and protocol development, including sample size validation (Module 3)
☐ Maintenance of blinding and procedures for unblinding for analysis (Module 3)
☐ Development and review of Case Report Forms (CRFs) (Module 4)
☐ Review of database specification and data validation plan (Module 4)
☐ Central/statistical monitoring (Module 4)
☐ SAE reconciliation (Module 4)
• Use and validation of non-CRF data (e.g. central laboratory data) (Module 4)
☐ Coding free text fields (Module 4)
☐ Data lock and processes for obtaining the data for analysis (Module 4)

General GCP

General GCP principles which extend to statistical processes
☐ Quality systems, written procedures etc. (Module 2)
☐ Training documentation (Module 2)
☐ Trial master files and archiving (Module 2)
Core GCP material
☐ Introduction to GCP (Module 1)
☐ UK regulations, frameworks and guidance and ICH GCP (Module 1)
☐ Principles of GCP (Module 1)
☐ Roles and responsibilities (Module 1)
☐ Informed consent (Module 1)
☐ Safety reporting definitions (Module 1)
☐ Serious breaches (Module 1)

Example slides

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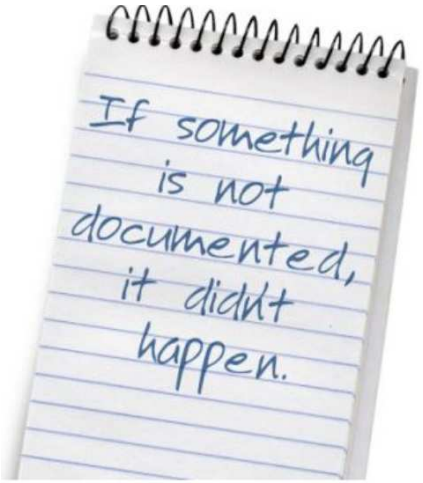
Trial Master File

The TMF **must** be a robust record of all aspects of the clinical trial and it **must** be kept up to date.

The TMF may be paper and/or electronic.

It **should** contain sufficient documentation to adequately reconstruct trial activities and key decisions without needing the trial team to be available.

Periodic auditing of the TMF can ensure it is kept up to date.



The TMF is the basis for MHRA inspection.

Protocol development

Statistical input to protocol development is **recommended**; evidence and/or procedures **should** be in place to accomplish this.

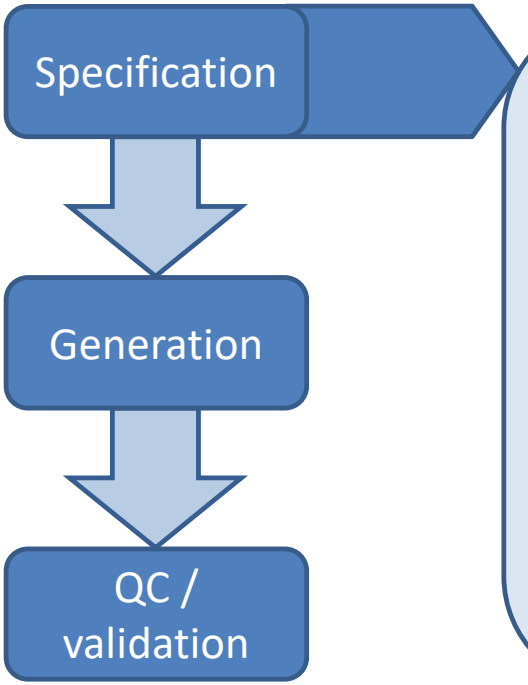
The statistical aspects of the design and analyses in the protocol **must** be followed, therefore it is **recommended** that the statistician approve and sign the trial protocol.

Protocol amendments **should** be reviewed by a statistician to assess the impact on the trial design and analysis. A process **should** be in place ensure that this occurs.

The role of the statistician in designing the trial and writing sections of the protocol may be examined during GCP inspections.

Randomisation

Methods of randomisation that cannot be verified and reconstructed at a later date must be avoided.



- Development of a 'randomisation specification' that contains key features of the randomisation is **recommended** - a statistician is usually involved in determining this specification.
- The specification **should** detail the randomisation method (e.g. random permuted blocks, minimisation with random element), block sizes or random element, stratification factors, approach for delivery (e.g. web-based, voice recognition, envelopes) etc.
- Distribution of the randomisation specification **should** be restricted.
- The trial protocol **should** describe the method of randomisation and any stratification factors – but ***not*** details which could facilitate allocation prediction (e.g. block size(s)).

Blinding

Procedures (e.g. documented access restrictions) **should** be implemented to control the randomisation schedule, or documents containing treatment information, to prevent accidental or deliberate unblinding. This **must** be strictly enforced for blinded protocols. FA2

A blinding/unblinding plan can be helpful to document who will have access to unblind data and when, or under what circumstances.

Screen shots or audit trails of access permissions can be used to evidence access control.

Slide 37

FA2 MIght want to mention emergency unblinding and unblinding to report SUSARs - the means to control unblinded data/information. Also care on distribution of reports - e.g. SUSARs, listing from IRT systems that could unblind, DMC reports etc. Consideration for a blinding/unblinding plan - who is blinded, who is unblinded and when and what circumstances.
Fisher, Andrew, 15/03/2021

Database/Dataset Lock

Provision of the 'final data for analysis' **should** follow a formal database/dataset lock process.

A signed checklist is **recommended** to confirm completion of activities prior to database lock. Example activities that may be included are:

- ✓ All data queries have been closed, if not, decisions documented
- ✓ All monitoring and SDV activities have been completed
- ✓ Reconciliation of safety data complete
- ✓ Coding review complete
- ✓ Statistical Analysis Plan (SAP) has been approved

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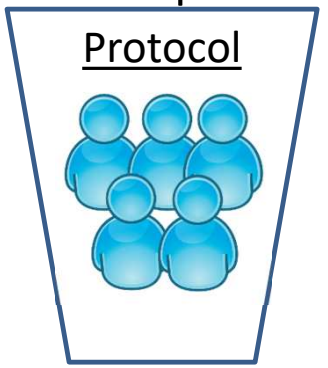
Per-protocol population

The decision for excluding subjects from the PP set **should** be documented so it is clear who made the decision and when it occurred, as it **should** be undertaken prior to any efficacy analysis.

- For blinded trials this **should** be undertaken prior to unblinding.
- For open-label trials it is **extremely important** that analysis populations are pre-defined before access to any data.



It is important the final study report contains a listing or summary of all significant non-compliances that occurred during the trial and how these contributed to the analysis.

Interim Analyses

Interim analysis may be planned in the protocol as part of a formal review. They are an essential part of some trial designs, e.g. group sequential and dose escalation trials.

The timing and purpose of an interim analysis, together with full details of stopping rules (e.g. for futility, safety, efficacy) **should** be carefully described in the protocol.

For blinded trials, unblind interim analyses **should** be conducted, where possible, by a statistician who will have no further involvement in trial conduct or the final analysis.

Interim analyses **must** be conducted as specified in the protocol. The decision to cancel an interim analysis **must** be documented as a protocol amendment.

Datasets used for interim analyses **must** be retained to provide an audit trail.

Some Referenced Guidance

UKCRC Registered Clinical Trials Units

JAMA | Special Communication JAMA. 2017;318(23):2337-2343. doi:10.1001/jama.2017.18556

Guidelines for the Content of Statistical Analysis Plans in Clinical Trials

Carrol Gamble, PhD; Ashma Krishan, BSc; Deborah Stocken, PhD; Steff Lewis, PhD; Edmund Juszczak, MSc; Caroline Doré, BSc; Paula R. Williamson, PhD; Douglas G. Altman, DSc; Alan Montgomery, PhD; Pilar Lim, PhD; Jesse Berlin, ScD; Stephen Senn, PhD; Simon Day, PhD; Yolanda Barbachano, PhD; Elizabeth Loder, MD, MPH

VALIDATION OF STATISTICAL PROGRAMMING

Validation of Statistical Programming
Gamble, Dore, Stocken, Lewis, Juszczak, Bradburn , Williamson, Kean

A proposed charter for clinical trial data monitoring committees: helping them to do their job well

DAMOCLES Study Group*

SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials

An-Wen Chan,[1] Jennifer M Tetzlaff,[2] Peter C Gøtzsche,[3] Douglas G Altman,[4] Howard Mann,[5] Jesse A Berlin,[6] Kay Dickersin,[7] Asbjørn Hróbjartsson,[3] Kenneth F Schulz,[8] Wendy R Parulekar,[9] Karmela Krleža-Jeric,[10] Andreas Laupacis,[11] David Moher[2 10] BMJ | RESEARCH METHODS AND REPORTING

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Conclusions

- This project provides and accessible, comprehensive, reviewed and piloted GSP Training package
- Freely available and ready for national adoption and certification
- Dedicated training tailored to statisticians working in clinical research, particularly the clinical trials arena, will
  - ➢ strengthen knowledge of relevant regulatory requirements
  - ➢ strengthens GCP interpretation and implementation
  - ➢ encourage good practice at a high level
  - ➢ Lead to transparent and reproducible statistical activity, as is reviewed upon inspection

Acknowledgements

- PMG
  - Deborah Stocken, Helen Mossop, Emma Armstrong, Steff Lewis, Susan Dutton, Claire Peckitt, Carol Gamble
- UKCRC CTU Statisticians Operations Group
- Pilot CTUs
  - Leeds, Newcastle, Edinburgh, Oxford, Royal Marsden, Liverpool
- Exeter University
- NIHR Statistics Group
- Andrew Fisher, MHRA
- John Castledene, NIHR Learn