Final Report: Efficient / Innovative Delivery of NIHR research

GSP: Good Statistical Practice (Good Clinical Practice for Statisticians)

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Total word count: 2072

1. Abstract

Statisticians are fundamental in ensuring clinical trials are conducted with quality, transparency, reproducibility and integrity. Conduct of clinical trials according to Good Clinical Practice (GCP), an internationally recognised, ethical and quality standard, is a regulatory requirement. Statisticians are required to undertake training on GCP but existing training is generic and, crucially, does not cover statistical activities. This results in statisticians undertaking training mostly unrelated to their role and variation in awareness and implementation of relevant regulatory requirements with regards to statistical conduct.

The need for role-relevant training is recognised by the HRA, MHRA and MRC as well as the UKCRC Registered CTU and NIHR Statistics Groups. The Good Statistical Practice (GCP for Statisticians) project is an NIHR funded project to develop and deliver role-specific GCP training tailored to statisticians. Training materials have been developed based on MHRA GCP and cover legislation and guidance for best practice across all clinical trial processes with statistical involvement, incorporating existing UKCRC guidance on analysis plans, validation of statistical programming and data sharing. The training contains exercises and real-life scenarios to bridge the gap between theory and practice. Comprehensive feedback from pilot work with UKCRC CTU and NIHR Statisticians has been incorporated.

An accessible, comprehensive, piloted training package has been developed tailored to statisticians working in clinical research, particularly the clinical trials arena. The training is freely available for national and international adoption. This training will encourage best practice, leading to transparent and reproducible statistical activity as required by regulatory authorities.

2. Introduction

Statisticians play a crucial role in clinical trials research across all stages of design, delivery, analysis and reporting. The key role of statisticians is recognised by regulatory agencies[1,2,3] and funding bodies.

Good Clinical Practice (GCP) is an international quality standard which applies throughout all stages and across all disciplines involved in clinical trials [3,4]. All research staff should have training in GCP and an awareness of GCP requirements in relation to their role[5,6]. Statistical conduct requires compliance with GCP to ensure quality, transparency, reproducibility and integrity to ensure participant safety. Adherence should be demonstrable across all statistical processes of the trial. Statisticians involved in clinical trials of investigational medicinal products (CTIMPs) must undertake GCP training[7] and whilst not a legal requirement for non-CTIMPs, research should be conducted such that the safety of research participants is protected and data generated are credible and reliable.

Despite the recognised key role of the statistician, GCP training undertaken by most academic statisticians is generic and, crucially, does not cover activities related to their role. Nor is GCP training specific to statistical principles described by ICH-E9[1], MHRA GCP[3] or MRC GCP[4]. This lack of focused GCP training can result in poor awareness of the relevant regulatory requirements and recommendations for good practice. Within the statistical community there is a lack of clarity regarding the practical interpretation of GCP, despite receiving GCP certification.

Statisticians, as with other disciplines, need role specific training and guidance to be able to instigate and deliver clear and consistent statistical processes compliant with GCP recommendations. The need for role-specific training is supported by the Health Research Authority (HRA) and the MHRA who acknowledge that GCP training does not need to follow a generic syllabus or format and can be tailored to individuals' roles and responsibilities[5,6].

The UK Clinical Research Collaboration (UKCRC) Registered Clinical Trials Unit (CTU) Statisticians Operational Group raised GCP training for statisticians as a high-priority training gap. This report describes the development of an accessible, comprehensive, piloted Good Statistical Practice (GSP) training package tailored to statisticians working in clinical research, particularly the clinical trials arena. The

training equips statisticians with relevant regulatory knowledge, strengthens GCP interpretation and implementation in relation to statistician responsibilities. This training is directly relevant to all statisticians working in the medical arena, and is freely available for national and international adoption.

3. Methods

Review of Current GCP Training

Statistical activities and processes are not covered explicitly by existing GCP training accessible to those working in the NHS, UK universities and other publicly funded organisations involved in conducting clinical research. A survey of senior statisticians across the UKCRC CTU network identified current training practices and elicited opinion of training preferences.

Design and Development of GSP Training Material

The content of the training material was initially based on feedback from the UKCRC survey and experience of the co-applicant team and further developed utilising the MHRA GCP Guide[3]. The MHRA GCP Guide details legislative requirements and processes compliant with the principles of GCP specific to the conduct of CTIMPs in the UK. Other guidance documents and journal articles relevant to GCP or good statistical practice are included and referenced[8-12] as appropriate.

In the first instance, areas directly applicable to the roles and responsibilities of a clinical trial statistician were identified, followed by areas where there would be an expectation for statistical involvement or oversight; either because this was stated explicitly by MHRA or as identified through UKCRC CTU Statistics group activities. Activities were conducted over a number of UKCRC CTU Statistics group bi-annual meetings attended by 1 or 2 senior statisticians from each of the 45 UKCRC CTUs registered at that time. Activities focussed on the practical implementation of specific GCP requirements based on real-life scenarios and provided further iterations of the material prior to piloting.

During initial piloting, it became apparent that there was a desire for training to be stand-alone, as opposed to an adjunct to existing GCP training, which resulted in additional generic modules on core GCP principles to be developed.

From the outset, it was acknowledged the delivery of the training material would need to be flexible, including face to face as well as e-learning formats, to address differing statistical environments.

Critical Review and Piloting

Following development, the training material was piloted as small group, face to face training in five UKCRC Registered CTUs, intended to encourage discussion regarding practical implementation against CTU-specific standard operating processes. A senior statistician within each CTU delivered this face-to-face training to their statistics teams collating informal, detailed feedback to identify gaps or ambiguities.

Pilot activity was then conducted with NIHR statisticians to ensure the training remained relevant to statisticians conducting research outside of the UKCRC Registered CTU network. A day long training course was then delivered by members of the development team to statisticians working on non-clinical trial NIHR research. Training material was interjected with small group exercises and structured, anonymous feedback (Appendix 1) was collated.

The format and content of the training was finalised at break-out sessions of the UKCRC CTU Statistics Groups and the NIHR Statistics Group meetings, again collating structured, anonymous feedback.

4. Results and Conclusions

Review of Current GCP Training

An initial scoping exercise with UKCRC CTU Statisticians highlighted that, although interesting and research related, the GCP training statisticians received was felt to be unrelated to their statistical role. All but one person, in a meeting attended by at least 1 senior statistician from each of the 45 UKCRC CTUs registered at that time, felt there was a need for more role specific training. A survey of 45 statisticians representing the 45 UKCRC CTUs confirmed the need and clear desire for the development of a dedicated GCP training for statisticians (Appendix 2, Table 1). The majority of responders, 34/45 (76%), were senior statisticians responsible for designing trials and supervising analyses; 11/45 (24%), were statisticians

responsible for analysing trial data. Consequently, 22 (49%) responders had worked in clinical trials for more than 10 years; 10 (22%) 5-10 years; 9 (20%) 1-5 years and 4 (9%) <1 year. Thirty-nine (87%) responders worked on CTIMP trials.

One responder had not received any GCP training, but of those that had, 21/44 (48%) reported they had received certified GCP training and 19 (43%) received in-house training. Not exclusively, 15 (34%) attended NIHR certified face-to-face GCP training, 11 (25%) NIHR certified online GCP training, 5 (11%) attended Institute of Clinical Research (ICR) certified online training. NIHR GCP training is designed for individuals involved in the conduct of studies at research sites and NIHR acknowledge their training will not prepare those who have responsibility for other elements of a study.

Crucially, of 44 recipients, only five (11%) considered the GCP training they had received was highly relevant to their role; and only seven (16%) thought it helped them understand GCP requirements related to their role. The development of a dedicated GCP training course for statisticians was supported by 30/44 (68%); only 4 (9%) thought there was no need for a dedicated GCP training course; 10 (23%) were unsure.

Respondents were asked to choose their preferred form(s) of GCP training with 25/45 (56%) respondents choosing online; 20 (44%) face-to-face; 6 (13%) reading/workbook based; 4 (9%) reported no preference. Preferred audience(s) were 31/45 (69%) statistician only; 13 (29%) multi-professional but restricted to CTU teams; 4 (9%) multi-professional and un-restricted.

Design and Development of GSP Training Material

A comprehensive set of training slides has been developed to provide an introduction to GCP for statisticians involved in the conduct and analysis of clinical research in the UK. The training provides a high-level overview of GCP requirements and recommendations for best statistical practice. Group activities in a face-to-face small group teaching environment provide an opportunity to consider how GCP principles can be implemented in line with local statistical practice, including consideration of risk proportionate approaches given the variability in trials portfolios across CTUs. References are provided to sign-post to more in-depth guidance[8-12]. The training material has been developed by an experienced team of statisticians

with knowledge of UK regulators, specifically MHRA and TransCelerate (www.transceleratebiopharmainc.com), and funders, specifically NIHR, and in consultation with NIHR Learn and MHRA.

The training consists of five modules (Appendix 2, Table 2) which focus on GCP requirements or recommendations directly related to statistical activities, or activities which would usually require some statistical involvement. Additional topics include those applicable to staff working in research more generally, but of which statistical staff should have an awareness. General GCP principles are included to allow the training to be stand-alone. A modular approach follows the logical order of the progressive stages of a clinical trial, from trial design through to data analysis and reporting. The final module (Module 5) contains content most relevant to statistical programming and analysis incorporating the recommendations from NIHR UKCRC Validation of Statistical Programming project[10]. Training certificates document specific modules attended.

The modular format allows flexibility regarding delivery (face to face or e-learning) to supplement usual local GCP training practices. The face-to-face training material has been designed for delivery within statistics teams where the lead training provider is an experienced researcher with a good understanding of local processes, so discussions can be tailored against local standard operating procedures for translation into practice. Face to face training can take 2 to 3-hours to complete, including exercises and discussion. Translation of the training material to e-learning is crucial for accessibility. E-learning is essential for statisticians working in research teams but isolated form other statisticians, allows immediate access for new statisticians and allows accessible continued professional development.

Critical Review and Piloting

During the development phase, updates were provided and feedback received at 6-monthly meetings of the UKCRC CTU Statistics Group. This feedback provided direction to both the content and format for presentation.

A draft version of the complete training package was piloted through small group face to face training in five CTUs (Oxford, RMH and ICR-CTSU, Edinburgh, Leeds, Newcastle) and took approximately 2 hours to deliver, up to 3-hours including exercises and discussion. It has received overwhelmingly positive feedback: *“this is*

a really valuable tool to add to our training"; "something the stats community definitely needs and pleased that this is being taken forward"; "all-in-all that was a very positive experience"; "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 engagement was particularly highlighted: *"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."* as was the relevance to new starters: *"I wish I'd had this when I first started out".* The feedback was extensive and detailed including suggested amendments to content, presentation and language in order to clarify ambiguities. It was also suggested that i) training certificates could be provided, ii) core GCP could be incorporated to save having to complete two courses and iii) frequency could be every 2 years.

The training was summarised at an invited parallel session of the NIHR Statistics Group annual meeting to assess the applicability outside of the UKCRC Registered CTU network. Feedback from group work (Appendix 2, Table 3) demonstrated that every group either 'strongly agreed' (5/11) or 'agreed' (6/11) that the training material was relevant to their role. The majority, (82%) 'strongly agreed' (6/11) or 'agreed' (3/11) that the training increased their learning and understanding of GCP requirements in relation to their role.

A standalone, day-long, small group teaching session was delivered by members of the development team, to staff in an external unit working on non-clinical trial NIHR funded research, including statisticians and data management staff. Fourteen of the attendees provided formal written feedback (Appendix 2, Table 3): all would recommend the session to a fellow researcher, four scored the session 5/5 (excellent), the remainder scoring 4/5; 13/14 respondents 'strongly agreed' or 'agreed' the training material was relevant to their role and all 'strongly agreed' (7/14) or 'agreed' (7/14) the training increased their learning and understanding of GCP requirements in relation to their role. Useful, supportive comments included "*far more relevant to 'real life' than basic GCP training", "essential info for trials researchers", "informative, relevant, good structure", "comprehensive"* and *"this course should be made available to anyone using /collecting data rather than just statisticians. All of*

the people who work with statisticians should work as a team and therefore be offered similar training opportunities where roles/activities overlap".

5. Dissemination

The Good Statistical Practice training materials will be freely available and accessible through a variety of portals:

1. to CTUs via the UKCRC online platform https://www.ukcrc-ctu.org.uk/
2. to NIHR researchers via the NIHR Learn platform https://www.nihr.ac.uk/health-and-care-professionals/learning-and-support/good-clinical-practice.htm
3. worldwide via email contact directly to the University of Leeds medctrur@leeds.ac.uk

The Good Statistical Practice training will be launched in a UKCRC led TMRP webinar in June 2021 when materials will be uploaded to the identified platforms.

An oral presentation at the International Clinical Trials Conference[13], describing the need for the training, the development and pilot work and outlining the final content and modules, initiated wider dissemination activities and global awareness of the training. The material is conducive as pre- or post- conference training at relevant statistical and/ or clinical trials conferences.

Further dissemination will be through planned publication in a clinical trials journal. The training will be promoted via news pages and Twitter accounts of involved CTUs, the UKCRC Statistics Group, the NIHR Statistics Group and the TMRP network.

6. Acknowledgments

The authors would like to thank statisticians from the UKCRC CTU network, UKCRC CTU Statistics Oversight Group, NIHR Statistics Group who took part in discussions and pilot work. We would specifically like to thank staff of the University of Exeter for their engagement in day-long training. Thanks also to NIHR Learn and MHRA for their engagement and support.

Funding

This project is funded by the National Institute for Health Research (NIHR) CTU Support (Efficient Trial Conduct) Funding scheme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Contribution of Authors

Deborah Stocken, Professor of Clinical Trials Research and Head of Statistics, Leeds CTU, developed the grant application; had overall responsibility and oversight of the project; developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Helen Mossop, Statistician, Newcastle University, was partially funded through this grant and developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Emma Armstrong, Head of Quality Assurance, Leeds CTU, developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Steff Lewis, Professor of Medical Statistics, Edinburgh CTU, developed the grant application; developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Susan Dutton, Associate Professor of Clinical Trials, Oxford CTU, developed the grant application; developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Claire Peckitt, Lead Statistician, Royal Marsden CTU, developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Carrol Gamble, Professor of Medical Statistics, Liverpool CTU, developed the grant application; developed, piloted and reviewed all training material; wrote and reviewed final report and publication.

Julia Brown, Professor of Clinical Trials Research and Director of the Leeds CTU, reviewed the grant application, training materials, final report and publication.

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8. Appendices

8.1 Appendix 1: Structured Feedback Form

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Good Statistical Practice Project: Feedback Form

Thank you for attending the Good Statistical Practice Project Breakout Session today. We'd like to hear about your current GCP training and the GSP training material which was introduced at this session. Your responses will be valuable in updating and improving the course content/ format prior to it being finalised and released in 2019.

Where asked for your views please be as open as you can and provide as much detail as possible. Your individual responses will remain strictly confidential and anonymous.

1. What is your primary role? *Tick all that apply*
☐ Statistician analysing data
☐ Senior Statistician designing studies and supervision of analysis
☐ Other, please specify

2. Which type(s) of clinical research projects do you work in? *Tick all that apply*
☐ Clinical trials
☐ Observational / cohort studies
☐ Systematic reviews / evidence synthesis
☐ Other, please specify

3. What GCP training you have received? *Tick all that apply*
☐ None to date
☐ Post-graduate /academic qualification related to clinical trials
☐ GCP training – certified
☐ GCP training – not certified
☐ Other, please specify:

4. How often do you renew/revalidate?
☐ every 2 years
☐ every 3 years
☐ every 5 years
☐ Other, please specify:

5. How relevant was your current GCP training material to you in your current role?
☐ Highly relevant
☐ Relevant
☐ Of some relevance
☐ Not relevant
☐ Not sure

6. Did your current training help you understand GCP requirements in relation to your current role?
☐ Fully
☐ Partially
☐ Not at all
☐ Not sure

Please Turn Over...

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7. **Following the session today, please indicate your level of agreement with the statements below:**

	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
a) The planned GSP training material is relevant to my role					
b) The planned GSP example exercises are relevant to my role					
c) The planned training content will increase my learning and understanding of GCP requirements in relation to my role					
d) I will be able to apply new learning / skills					
e) The session was clear and well presented					
f) The session was interesting and relevant					

8. **What aspects of the planned training material would you find most useful/ relevant?**

9. **And least useful/ relevant?**

10. **How could we improve the training?**

11. **Would you prefer face to face or online training?**

12. **Any comments following the session in relation to what we are trying to achieve?**

Thank you for completing the feedback form.
Please leave it behind after the session or hand it to one of the session facilitators.

8.2 Appendix 2: Tables

Table 1: Survey Responses per CTU

	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%
Relevance of GCP training to role		
Highly relevant	5	11%
Relevant	10	23%
Some relevance	25	57%
Not relevant	3	7%
Not sure	1	2%
How much did training help you understand GCP requirements in relation to your role		
Fully	7	16%
Partially	31	70%
Not at all	5	11%
Not sure	1	2%
Do you think statisticians need a dedicated GCP training course		
Yes	30	68%
No	4	9%
Not sure	10	23%
Preferred form of GCP training*		
Online only	25	56%
Face-to-face only	20	44%
Reading based	6	13%
No preference	4	9%
Preferred audience(s) for GCP training*		
Role specific (statistician)	31	70%
Multi-professional - restricted to CTU teams	13	30%
Multi-professional - not restricted	4	9%
Not answered	1	

* Not mutually exclusive

Table 2: Training Topics and Modules

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)
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 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)

Table 3: Quantitative feedback from small group Pilot work

	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%

9. Conflict of Interest Declaration

No conflicts of interest to declare.