

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 – Summary of responses to consultation document MLX 328

Introduction

The MHRA consulted on the proposed amendments to the Medicines for Human Use (Clinical Trials) Regulations 2004 S.I. 2004/1031 during a 12-week period from 15 November 2005 to 7 February 2006. It distributed the consultation document (MLX 328) to over 2000 stakeholders and received responses from small and large pharmaceutical companies, contract research organisations, industry associations, laboratory services, ethics committees, NHS hospital trusts, primary care trusts, Royal Colleges, the Medical Research Council and other organisations representing academic researchers, charities supporting publicly funded research, individual investigators and patient associations.

Of the 75 responses, 41 said no comment and 34 provided specific comments of which 3 stated they had no concerns and 8 voiced concerns about three specific issues. The summary below lists the issues and concerns raised, the comments and MHRA responses are set out in Annex A.

Further guidance

Most of the comments asked for additional guidance on the following issues:

- Retention time for ethics committees' documents (13)¹;
- Definition of serious breach of GCP that has to be reported to MHRA (11);
- Specific modalities that will apply to non-commercial trials (11);
- Format and content of the investigator's brochure (6);
- Content of the trial master file (4);
- Format of new requirements for the manufacturing authorisation (2);
- Scope of the exemption for packaging and labelling (1);
- Update of the reference to the Declaration of Helsinki (1);
- Fee levels for marketed products used off label (1);
- Communication between MHRA and ethics committees (1); and
- The consequences of receiving an infringement notice (1).

In response to these requests MHRA has agreed to provide further guidance on the areas that need clarification.

Specific questions

For the following proposals respondents asked whether:

- A manufacturing authorisation was needed for distribution of IMPs? (1);
- The GCP Directive applied to marketed products in clinical trials? (1);
- The exemption for hospitals and clinics applied to reconstitution of radiopharmaceuticals? (1);
- A sponsor could delegate the duty to report to the MHRA? (2);
- The GCP Directive applies the same standards to generic medicines? (1);and
- There is any exemption from the requirement to have a QP release an IMP? (1).

Responses to these questions are included in Annex A.

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¹ The number in brackets indicates the number of respondents raising that issue.

Concerns

The three specific concerns raised were:

- The impact of the GCP Directive on those currently conducting unauthorised trials (2);
- Additional cost and bureaucracy (4);
- Changes to the wording of the principles of GCP (2).

MHRA has considered the above concerns:

- Those responsible for research in the NHS have tried to identify any trial of a medicine not yet authorised by MHRA. Few if any should be being conducted without an authorisation: they would be infringing the Clinical Trials Regulations.
- The consultation document specifically sought information on increased costs and bureaucracy that might result from the proposed amendments. No respondents provided specific examples of how the proposed provisions would increase costs or bureaucracy; the RIA provided a detailed description of the increased requirements for those not currently conducting trials to GCP standards.
- The MRC and a pharmaceutical company were concerned that confusion might arise because the GCP Directive will change the wording of the principles of GCP as they are described in the ICH GCP guideline. Following representations on this issue, the Commission indicated that they must retain the language in the legal texts of the Clinical Trials Directive and the GCP Directive.

RESPONSES TO CONSULTATION LETTER (MLX 328)

Item	Organisation	Summary of reply	MHRA Comments
1	STL (Seven Trent Laboratories) Howard Court, Manor Park Runcorn, CHESHIRE WA7 1SJ	No comments	
2	Dr KRH Adams Lever Chambers Centre for Health BOLTON BL1 0JR	Suggested that there need to be some discussion about the good that new drug treatment has achieved. Has been in the NHS for 30 years and have seen tremendous progress in the treatment of many illnesses. Almost all of these treatments have been developed by the drug industry. How about some credit? If the drug industry is not allowed to advertise and make a profit what happens if they give up. It is already obvious that research is more difficult to organise in the UK and is thus being done elsewhere. There needs to be some balance. Reply may be made freely available.	a) the Government works closely with industry in the UK e.g. The Pharmaceutical Industry Competitiveness Task Force (PICTF), MHRA/ABPI meetings, Datapharm all of which recognise the major contribution of the industry. b) The Government is trying to create an environment for the commencement and conduct of clinical trials that protects patients without inhibiting research on essential new medicines. c) One of the results of the Clinical Trials Directive is to focus attention on how to reduce administrative burden and streamline the procedures for commencing clinical trials. The system needs more time to bed in.
3	Laboratories for Applied Biology Limited 91 Amhurst Park LONDON N16 5DR	No comments	

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4	Joanne Charles Head of Medicines Management Charnwood & North West Leicestershire PCT Woodgate LONGBOROUGH LE11 2TZ	No comments	
5 ²	Herisse Limited 20 Hersham Centre Walton on Thames SURREY KT12 4HC	No comments	
8	Dr J.P. Edmondson-Josh Director Portsmouth City Teaching PCT Finchdean House Milton Road PORTSMOUTH PO 3 6DP	No comments Reply may be made freely available.	
9	Professor P.G. Sammes MEDAC Limited Brunri Science Centre Coopers Hill Lane ENGLEFIELD GREEN TW20 0JZ	No comments Reply may be made freely available.	
10	Dr T.L. Jones N & E Devon Ethics Committee, Old Kenn Ward RD & E Hospital EXETER	No comments	

² Where the numbering sequence is out of order it indicates that a respondent asked that their response should not be made publicly available.

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11	Drs Jason Kendall & Mike Shore Joint Chair, Frenchay REC c/o North Bristol NHS Trust BS16 1JE	No comments	
12	Panspermia Microbiology Unit A1, Mildmay Industrial Est. Foundry Lane, Burnham-on- Crouch, ESSEX CM0 8SH	No comments	
13	Mr C. Curtis Head of Pharmaceutical Services Burton Hospitals NHS Trust BURTON-upon-TRENT DE13 0RB	No comments	
14	Miller & Miller (Chemicals) Ltd Unit 3, Burnside Ind. Estate 49-53 Roebuck Road Hainault IG6 3UG	No comments	
15	M-Scan Limited 3 Millars Business Centre Fishponds Close Wokingham, BERKS RG41 2TZ	No comments	
16	British Cardiac Patients Association	No comments	

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17	North Wales Central REC Room 1038 Conwy & Denbighshire NHS Trust, Glan Clwyd Hospital Bodelwyddan, Denbighshire LL18 5UJ	No comments	
18	Dr Myles Nelson LEAO Consultant in R&D Postgraduate Medical Centre Antrim Area Hospital 45 Bush Road ANTRIM BT41 2RL	No comments	
19	Professor R.C. Spiller Wolfson Digestive Diseases Centre The University of Nottingham NOTTINGHAM NG7 2UH	Main concern refers to the particular sort of trial which is a single centre "Proof of Concept" study with only one main investigator. Finds it excessively bureaucratic to insist on an Investigator's Brochure and accept it where it is entirely relevant to a multi-centre study which involves many other investigators. Exception should be made, say if there is only a single investigator it would be sufficient to put details of drug characteristics and safety in the protocol and ethics submission and not to generate a separate investigators brochure. Reply may be made freely available.	<u>Guidance on the investigator's brochure (IB)</u> The GCP Directive does not introduce any new requirements for IBs; it allows the Summary of Product Characteristics to be substituted for certain trials with marketed products. Section 4.1.5 of Commission guidance on applications to the competent authority (CT-EN-04) gives guidance on the investigator's brochure: It provides that the Summary of Product Characteristics (SmPC) may be part of the IB or replace it where the investigational medicinal product has a marketing authorisation.
20	Homeyman Group Limited Harmire Enterprise Park Barnard Castle DL12 8BN	No comments	

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21	Interpharm Limited Unit1, 99b Cobbold Road Willesden, LONDON NW10 9SL	No comments	
22	Cathie Stokes North West Multi-Centre Research Ethics Committee Gateway House Piccadilly South MANCHESTER M60 7LP	No comments	
23	Professor Ajay Vora Dept. of Paediatric Haematology Sheffield Children's Hospital SHEFFIELD S10 2TH	<p>From the perspective of a Chief Investigator of an investigator led childhood leukaemia trial, there are a number of issues still not entirely clear and others where the MHRA need to apply the regulations pragmatically to investigator led trials, or such trials will get mired in a nightmare of bureaucracy and red tape which will lead to worsening rather than an improvement in patient safety.</p> <p><u>Investigators brochure:</u> Most cancer trials contain numerous drugs which are not themselves being tested but are being used as part of standard treatment within a clinical trial either without a UK licence (example Oncospar has only a German licence and is an essential part of the treatment of childhood acute lymphoblastic leukaemia so has to have a CTA even though the drug itself is not being tested as</p>	<p>a) <u>Investigator's brochure</u> The proposed regulation provides that the Summary of Product Characteristics (SmPC) may replace the IB where the investigational medicinal product has a marketing authorisation. The requirement to update applies to the IB but not the SPCs that replace them.</p> <p>When the IMP is identified in the protocol only by its active substance, the sponsor should elect one SPC as equivalent to the IB for all medicinal products that contain that active substance and are used at any clinical trial site.</p> <p>For an international trial where the medicinal product to be used in each member state is the one authorised at a national level and the SmPC varies among member states, the</p>

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		<p>part of the current childhood ALL trial) or off label (example, many chemotherapy drugs do not have a paediatric specific licence).The paper says that an SPC is adequate as a substitute for an investigators brochure for a licenced product. Each UK product has a separate licence, so to use a variety of products of the same off-patent drug and formulation requires a copy of each manufacturers SPC. For "off patent" drugs this can be ever changing and numerous SPCs. A variety of products is necessary due to NHS contacting rules, which prohibit a hospital using a non-contract supply, unless the contract drug is unavailable. Although many drug contracts for NHS hospitals are now becoming national, rather than regional, they are still subject to annual change. The requirement for an annually updated SpC from each and every manufacturer of an off-patent drug would have enormous implications and a massive increase in work-load for investigator led cancer clinical trials.</p> <p>Exemption for hospital and health centre reconstitution from manufacturing regulations, this is where we can extemporaneously dispense (ie make a suspension from a licensed tablet) in house but not farm it out to a manufacturer who holds a "specials licence"</p> <p>As the specials licenced manufacturers we use also hold a "clinical trial manufacturing</p>	<p>sponsor should chose one SmPC to replace the IB for the whole CT.</p> <p>b) <u>Extemporaneously prepared specials</u>: The exemption for hospitals and health centres only applies to <u>packaging and labelling</u>. Reconstitution does not fall within the scope of manufacturing in the UK.</p> <p>c) <u>Unauthorised clinical trials</u>: The Clinical Trials Regulations (S.I. 2004/1031) is the only legal basis for conducting clinical trials in the UK since 1 May 2004. Prior to that there was an obligation to inform the licensing authority of all clinical trials. The holders of legal exemptions were contacted before the regulations came into force and were allowed to roll their exemptions over to become Clinical Trial Authorisations (CTA). Any clinical trial currently being conducted without a CTA is illegal and could have serious consequences for the sponsor.</p>

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		<p>authorisation" they are qualified to extemporaneously dispense for the trial. We, however, need a CTA for each of their products and each time the product batch is made the CTA has to be updated as it is effectively a "new unlicensed product".</p> <p>The standard of the "specials" is much higher than that produced in a hospital and so the exemption needs to be applicable to hospital, health centres and extemporaneously prepared "specials" from licensed "specials" manufacturers.</p> <p><u>Offences on CTA certification</u></p> <p>It is unfair to expect trials that started before the regulations came into force in May 2004 to be closed down due to lack of a CTA. The MHRA rolled over DDX certificates to CTAs, but under the old rules only drugs with no UK licence at all required DDXs. There are a lot of trials out there which will shut down if this was enforced. Also what is the position on trials where second line treatment is recommended but not part of the randomised trials, and data is collected. The second line drugs part of the trial or not? This needs clarification.</p> <p>Reply may be made freely available</p>	

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24	Dr G.D. Windsor MycoPlasma Experience 1 Norbuy Road, Reigate SURREY RH2 9BY	No comments	
25	Dr D.H. Keeling Chairman I.E.C. Plymouth Westelle Road DEVON PL20 6AS	No comments	
26	Dr David A. Walsh Chair N. Notts LREC	No comments Reply may be made freely available.	
27	A. Hensisy PDCA Roche Products Ltd Hexagon Place 6 Falcon Way Shire Park HERTS AL7 1TW	No comments	
28	Covance Laboratories Europe Ltd Otley Road Harrogate NORTH YORKS HG3 1PY	No comments	
29	Rev. Keith Lackenby 7 th Avenue Gainsborough LINCS DDN21 1EP	Broadly welcome the proposals in this document particularly those that seek to detect research fraud. A question of clarification regarding the rule that EC must retain documentation for 3 years. Is it correct in assuming that this means 3 yrs after completion of said trial? Correct in assuming this would be made explicit in the regulations as the disposal of documents before the completion of	<u>Retention of documents by an Ethics Committee</u> : The period is at least three years after the completion of the trial. This will be made explicit in the amended regulations

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		any trial would present serious problems to an EC asked to approve an amendment.	
30	Dr G. Meakin on behalf of Association of Paediatric Anaesthetists of GB & Ireland Royal Manchester Children's Hospital MANCHESTER M27 4HA	The proposal to amend the Medicines for Human Use (Clinical Trials) Regulations to implement the Commission Directive of Good Clinical Practice (2005/28/EC) seems reasonable and in line with policy in other EC Directives.	
31	Michele Caldwell Director of Pharmacy NHS Ayrshire & Arran Eglinton House Dalmellington Road AYR	No comments My reply may be made freely available	
33	Paul Kaiser Tendring PCT Kennedy House Kennedy Way CLACTON-ON-SEA Essex	No comments	
34	George Downie Director of Pharmacy & Medicines Management NHS Grampian Medicines Unit Westholme Woodend Hospital Queens Road ABERDEEN AB15 6LS	No comments Happy with the proposed amendments.	

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35	Dr P A Carson CIREC 6 Capenhurst Techonology Park Capenhurst, CHEATER CH1 6ER	Noted proposal for document retention time is a:- <ul style="list-style-type: none"> • minimum of 3 years for RECs • minimum of 5 yrs for medical records whereas industry standard for GCP study documentation is 15 yrs. Since this represents current practice no on-costs would result if 15yrs selected as the aim for all documentation and this would facilitate audits after the study had been completed and reached market place, or to check documentation after delayed SAEs. My reply may be made freely available.	<u>Retention time for REC records and medical records:</u> These times are minimum periods. It is expected that commercial sponsors will retain the records for longer periods voluntarily.
36	NHS Fife Hayfield House Hayfield Road KIRKCALDY KY2 5AH	No comments	
37	Dr Michael Philpot South London & Maudsley Institute of Psychiatry Denmark Hill LONDON SE5 8AZ	No comments	
38	Dr G.J. Baxter RDSU & DGRI NHS Dinkfrits & Galloway	Chapter 1 – Makes sense to consult not “stakeholder” Chapter 2 – All points make sense Chapters 3; 4; 5 & 6 – Agree Additional comments – agree Overall – no problem seem to be completely appropriate. My reply may be made freely available.	

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39	AstraZeneca UK Ltd Horizon Place 600 Capability Green Luton LU1 3LU	<p>My comments on the proposal : Specific comments:</p> <p>Declaration of Helsinki The GCP Directive references the Declaration of Helsinki 1996. Should this be updated to the Edinburgh Version 2000 including the two clarifications of 2002 and 2004?</p> <p>Chapter 2 Principles of Good Clinical Practice (1) Ethics Committees: we propose to add to the procedure a requirement that ethics committees retain documents for at least three years and have systems for exchange of information with the MHRA.</p> <p>Comment: The main RECs and MHRA should interact more and this is a step forward that is welcomed.</p> <p>(2) Investigator's Brochure: the original Regulations did not anticipate that the law would stipulate the format of the investigator's brochure. This is a document that draws together the data on the study of the medicine in humans, and it is designed to provide background information for the investigators. The proposed amendment would require that the brochure be prepared in a concise, simple, objective, balanced, non-promotional form.</p>	<p>a) <u>Declaration of Helsinki</u>: The GCP Directive refers to the 1996 version referred to in the recitals of the Clinical Trials Directive which is consistent with the version in the ICH guidance note on Good Clinical Practice. The 1996 Version was chosen because, at the time the Directive was agreed there was widespread debate about the proposed amendments in the 2000 version. The Amendment Regulations don't specify the version.</p> <p>b) <u>Retention of records by Ethics Committees</u>: The period is at least three years after the completion of the trial. This will be made explicit in the amended regulations</p> <p>c) <u>Template for IB</u>: MHRA will provide guidance and a mock/example template for the IB on its website) Clarification of when SmPC can be used instead of IB. Guidance will be provided on this.</p> <p>e) <u>Content of TMF</u>: The Commission will provide Guidance on this with the consensus of the Member States.</p> <p>f) <u>Retention of Medical Records</u>: MHRA will provide guidance on specific situations</p> <p>g) <u>Definition of end of trial</u>: The guidance on applications to the competent authority, amendments and end of trial (CT-EN-04) provides guidance on what constitutes the end of a trial.</p>

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		<p>Comment: Would be useful if the MHRA could produce a mock example/template so that sponsors have some guidance to follow</p> <p>Investigator's Brochure When is the SmPC appropriate? it isn't always as clear-cut as it might appear. It would be good to have this clarified in more detail.</p> <p>Sponsorship- Article 7 Sponsor may delegate aspects of a clinical trial while retaining overall responsibility. This is good.</p> <p>Chapter 4 Trial Master File and Archiving (3) Format of trial master file: the GCP Directive sets out new requirements about documents which are to be included in the master file reporting on the clinical trial and about how these documents are to be archived. We propose to amend the Regulations to reflect these new requirements. However, we are still waiting for Commission guidance on the content of the documents which are to be included; when this is published further amendment to the Regulations may be required.</p> <p>Comment: Would be useful for the MHRA to give set guidance on exactly what they require to see in the SMF/ISF. Would be useful to find out if the</p>	<p>h) <u>Persistent breach of protocol</u>: MHRA will provide guidance on the specific situations. Sponsor can ask for a 'for cause' inspection using the MHRA 'whistleblowers' procedure.</p> <p>Examples:</p> <ul style="list-style-type: none"> • Violations of eligibility criteria such that patient's are put at risk, or the trial design is invalidated; • Systematic failure to adhere to the schedule of events relating to patient's visits; • routinely failing to follow instructions for handling trial medication; • Systematically using incorrect patients information and/or consent forms; • Routinely failing to follow safety instructions given in the protocol; • Routinely failing to adhere to data recording/handling instructions given in the protocol.

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		<p>MHRA are talking with other agencies on what they expect to see and get a consolidated view of overall expectations</p> <p>Retention of medical records As well as specifying a time it would be good if some guidelines could be given about how to handle specific situations ? - What happens to files if patient moves GP? ? - What happens to files if patients leave the country?</p> <p>Paragraph 26: Need to define "end of trial".</p> <p>Paragraph 28 Needs more definition and guidance for persistent breaches of protocol e.g. studies that have scores of minor deviations, would be hard to know at which point to involve MHRA - which is a good idea in itself - but could lead to different thresholds/ tolerances across monitors and across various pharmas/CROs.</p> <p>Who would judge if patient safety had been put at risk? Also need more guidance on whether sponsor should involve MHRA when it becomes aware of the issue, or only if site does not rectify issues when sponsor has pointed them out and given site a chance to correct? If so what would be acceptable timelines?</p>	

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		<p>Falsification of trial data - should be separate and immediately reported - but is this suspected or proven? If suspected fraud, could sponsor request a "for cause" inspection of the site by the MHRA?</p> <p>Paragraph 31 Good idea and would help reduce administrative delays to study start up waiting for payments to be made</p>	
40	<p>Prof. Gordon Ferns Chair R&D Royal Surrey County Hospital Egerton Rd Guildford Surrey GU2 7XX</p>	<p>Chapter 1: 'Specific modalities' needs to be qualified with examples.</p> <p>Chapter 2: Should the retention of documents be qualified with a statement that documents should be retained for three years after the completion of the trial if this is the intent.</p> <p>Chapter 3: The clarification on exemption for a manufacturing authorisation is welcomed.</p> <p>Chapter 4: The clarification on retention of medical records is welcomed.</p> <p>Chapter 5/6: Further clarification on 'serious breach' would be helpful. How should persistent be interpreted. Do single breaches in several trials count as persistent? My reply may be made freely available.</p>	<p>a) <u>Specific Modalities</u>: The Commission will publish guidance on 'specific modalities' for consultation before finalising.</p> <p>b) <u>Retention of records by RECs</u>: The period is at least three years after the completion of the trial. This will be made explicit in the amended regulations</p> <p>c) <u>Serious Breach of GCP or protocol</u>: A definition of "serious breach" will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p>

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41	Dr Mary Fraser HO R & D Forth Valley Primary Care NHS Red Lodge, Old Denny Road LARBERT PK5 4SD	No comments	
42	Dr T. Clarke Chair, Joint Royal College Ambulance Liaison Committee c/o Royal College of Physicians 11 St. Andrews Place, Regents Park, LONDON NW1 4LE	No comments	
43	Professor Normal C. Nevin GTAC 6 th Flr, Welling House 133-155 Waterloo Road LONDON SE1 8UG	Chapter 1 – Specific provisions GTAC is interested in the provision that specific modalities are to be introduced with respect to manufacturing, trial documentation and archiving for trials conducted by academic researchers without the participation of the pharmaceutical industry. Looking forward to seeing MHRA's response to this work in progress. Additional requirements: Notification of site closure. Two options were proposed on action required by the sponsor if they became aware of a serious breach of GCP:- Option A: Requirement to notify MHRA. GTAC understands that this would enable sponsors to detect the problem, to implement a change strategy (which would include the option of site closure but could also include corrective action)	a) <u>Specific Modalities</u> : The Commission will publish guidance on 'specific modalities' for consultation before finalising. b) <u>Serious Breach of GCP or protocol</u> : A definition of "serious breach" will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)

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		<p>and to keep the site open with the problem rectified.</p> <p>Option B: Site closure. GTAC considered that might result in a black-listing of that investigator and/or site, and would not enable standards to be raised.</p> <p>GTAC considered the above options and judges that option a would be more desirable. Guidance for sponsors on what action to take would be helpful.</p>	
44	<p>James Wallace Yorkhill NHS Division Pharmacy Department Queen Mothers' Hospital Dalnair Street GLASGOW G3 8SJ</p>	<p>The Paediatric Chief Pharmacist Group fully support the proposals in MLX 328 My reply may be made freely available.</p>	
45	<p>Alison Campbell On behalf of NHS Argylla Clyde</p>	<p>No comments</p>	
46	<p>Mr Leonard Key LREC1 (Newcastle & North Tyneside) Newcastle NE2 4HH</p>	<p>No comments My reply may be made freely available.</p>	
47	<p>Dr John Watt Southport & Ormskirk Hospital NHS Trust Town Lane Kew Southport PR8 6PN</p>	<p>There are certain clinical trials, for instance when it is proposed that a drug is to be used outside its licensed indication. The table of charges does not always identify which is the appropriate fee and it may be that the protocol must always be submitted to CTU for an opinion but if possible the tables possibly be expanded to incorporate those situations.</p>	<p>a) <u>Fees for CTA</u>: MHRA will provide clarification on the level of fees for a product with a marketing authorisation used outside its licensed indications.</p>

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48	Lesley Lockhard Royal College of Physicians, Edinburgh 90 Queen Street, EDINBURGH EH2 1JQ	The College has few comments on the proposals to amend the regulations to comply with the provisions of the Commission Directive on Good Clinical Practice. The College supports efforts to improve and protect standards of research conduct, and has been instrumental in establishing a national panel to investigate research misconduct. However, in common with many other organisations, the College continues to have significant concern about the impact of the Commission Directive on non-commercial (largely university and NHS funded) research. This consultation document implies that there may be greater flexibility in the interpretation of the Directive than first suggested, and we will be pleased to comment more fully on the proposed guidance for “specific modalities” when it is available.	<u>Specific Modalities</u> : The Commission will publish guidance on ‘specific modalities’ for consultation before finalising.
49	Dr Joanna Nakielny Eli Lilly & Co. Lilly House, Priestley Road Basingstoke, HANTS RG24 9NL	No comments Reply may be made freely available.	
50	Berly Malone Royal College of Nursing 20 Cavendish Square LONDON W1G 0RN	No Comments	

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51	Pharmaceutical Society of Northern Island 73 University Street BELFAST BT7 1HL	Considered the proposals in MLX 328 and welcomes any amendment to clarify and streamline the Medicines for Human Use (Clinical Trials) Regulations 2004. The proposed changes should ensure the wellbeing of trial participants and ultimately enhance patient care. Supports the proposed amendments.	
52	Welwyn Clinical Pharmacology Ethics Committee	No comments.	
53	Medical Director British Heart Foundation 41 Fitzhardinge Street LONDON W1H 6DM	Not convinced that the proposed changes will not add substantial cost and bureaucracy to small academically led trials. The details of Article 1 will be very important and they are looking forward to seeing it when it becomes available. Reply may be made freely available.	<u>Cost and bureaucracy:</u> The consultation document sought information on additional costs for small academically led trials.
54	Virginia Gretton Nottingham Clinical Research Ltd Isaac Newton Centre Nottingham Science & Technology Park Nottingham NG7 2RH	Chapter 3 Manufacturing Conditions of holding a manufacturing licence: Interpretation of EU Directive 2005/28/EC in countries outside the UK assumes that distribution of drug is always performed by the same facility that manufactures and/or performs European QP release. As a result, regulatory authorities in France and Belgium demand to see a manufacturer's licence before they will agree to receive clinical trial medication. At present the MHRA is unable to issue a licence covering storage and distribution only. We ask that this oversight is rectified when a company offering a storage and distribution service can demonstrate:	<u>Distribution of IMPs:</u> The Directive 2001/20/EC is silent on distribution. This has been interpreted that an IMP is not intended to be generally distributed as with a licensed relevant medicinal product. There is no general authorisation required to store and distribute IMPs.

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		<p>1) Correct analysis and European QP release of clinical trial medication before delivery to the distributor's premises.</p> <p>2) Experience and training of the distributor's staff are adequate.</p> <p>3) Applicable sections of Good Manufacturing Practice are adhered to.</p> <p>4) The distributor's quality control procedures are of a high standard.</p> <p>5) Communication with the MHRA is satisfactory - for example, a successful Good Clinical Practice inspection, which included procedures relating to storage and distribution of clinical trial medication. Failure to correct this oversight will continue to prevent UK based companies competing on level terms with similar organisations within the EU. Reply may be made freely available.</p>	
55	<p>Dr Catherine Elliott Medical Research Council 20 Park Crescent London W1B 1AL</p>	<p>The MRC is strongly committed to ensuring that the safety of participants is paramount in the conduct of clinical research and recognises that the proposed amendments to the Medicines for Human Use (Clinical Trials) Regulations 2004 have been developed to promote the safety of participants in clinical trials.</p> <p>Good Clinical Practice</p> <p>In reviewing the amendments, we recognise that the alterations to the GCP requirements of sponsors are taken from the EU Directive and therefore are required to be included in UK</p>	<p><u>Principles of GCP:</u> MRC concerned that changing wording from ICH GCP guideline will cause confusion without benefits. Commission lawyers advised that ICH wording could not be used.</p> <p><u>Specific Modalities:</u> The Commission will publish guidance on 'specific modalities' for consultation before finalising.</p> <p><u>Serious Breach of GCP or protocol:</u> A definition of "serious breach" will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of</p>

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		<p>legislation. The principles in the existing Regulations are based on those agreed by the International Conference on Harmonisation (ICH) – the international standard agreed by Europe, the USA and Japan. We recognise that there is little difference in practice between the principles of good clinical practice specified in Directive 2005/28/EC and those in the existing UK Regulations. However, we would wish to be clear that MRC continues to uphold the principles of the ICH while recognising that the new Regulations will apply to specific circumstances. We are concerned that the change brought about by the Directive has no obvious benefits and may give the impression that the UK and Europe no longer uphold those standards.</p> <p>We note that guidance on "specific modalities" applicable to some non-commercial clinical trials is currently being prepared. As the largest public funder of clinical trials in the UK, the MRC would welcome the opportunity to participate in these discussions and comment on draft guidance at an early stage.</p> <p>Trial Master File and Archiving We welcome the potential flexibility inherent in Article 16 of the Directive which specifies that the content of the essential documents shall be in</p>	<p>GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p> <p><u>Retention of documents:</u> Article 17 of Directive 2005/28 Requires retention for at least 5 years or longer where required by other applicable requirements.</p>

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		<p>accordance with the specificities of each phase of the clinical trial. We trust that a proportionate approach to the required content of the master file for different types and phases of trial will be reflected in the Commission guidance and in any amendment to the UK Regulations.</p> <p>Notification of site closure The MRC recognises its duty to identify breaches of GCP in trials that it sponsors and to take appropriate action, including the closure of trial sites if patient safety is at risk. We are concerned, however, that without an unambiguous definition of what constitutes a serious breach of GCP, sponsors and inspectors may differ in their interpretation. In some circumstances, non-compliance with a protocol may be fairly trivial (e.g. patient recruitment slightly outside the specified age range in a pragmatic trial) and have no implications for patient safety. The normal approach would be take measures to improve compliance through staff and investigator training, and not to close the trial at that site. If site closure is deemed necessary to protect patients, we consider that a mechanism already exists to inform the MHRA of this under Regulations 24 or 30 and so an additional requirement is not necessary.</p>	

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		<p>Document retention</p> <p>One other area on which we would like to comment briefly is in relation to the requirement that ethics committees retain the essential documents relating to a clinical trial for three years. MRC guidance requires trial documentation to be retained for 20 years from completion of the project. This will include copies of submissions to and approvals from Research Ethics Committees (RECs). However, if there are other documents relating to the ethical approval process for a trial that are not available to the sponsor, it may be appropriate for RECs to retain these for a longer period than three years in accordance with other trial documentation. This may be of assistance in responding to any future query about the ethical review process.</p> <p>Reply may be made freely available.</p>	

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56	Louise Boniface Research & Development Co-ordinator Clinical Audit and Research Unit London Ambulance Service NHS Trust - HQ Annexe Ground Floor 8-20 Pocock Street London SE1 0BW	<p>Has a query regarding the consultation document MLX328: Consultation on implementation of the European Commission's Directive on Good Clinical Practice (2005/28/EC).</p> <p>In the 'Scope of the GCP Directive and proposed amendments' section, on page 1, the document states:</p> <p><i>"The 2005 GCP Directive applies to clinical trials of 'investigational medicinal products', in other words, Medicines which are being developed for human use."</i></p> <p>As far as it is understood, the Clinical Trials Regulations that are being amended here apply to <i>any</i> trial of a medicinal product where its efficacy is being measured, regardless of whether it was already marketed or still in development. That is to say, even if a marketed product was being trialled; if its efficacy was being measured (either within or outside of the terms of the Marketing Authorisation), we would be conducting a clinical trial and would therefore need to comply with the Clinical Trials Regulations.</p> <p>The paragraph copied above seems to imply that the GCP directive only applies to medicines under development (and not to trials of marketed medicines). Can you please clarify this?</p>	<p><u>Scope of Directive:</u> The Directive applies to marketed products because marketed products are included in the definition of an "investigational medicinal product" in Article 2 of Directive 2001/20/EC.</p>

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57	<p>Lesley E. Smith GE Healthcare Grove Centre White Lion Road Amersham, BUCKS HP7 9LL</p>	<p>Chapter 2 Principles of Good Clinical Practice: Investigator Brochure. Article 8 "The proposed amendment would require that the brochure is prepared in a concise, simple, objective, balanced, nonpromotional form. For a marketed product, the Summary of Product Characteristics could substitute for it. Also, the amendment would require updates to the brochure at least annually or for new safety concerns".</p> <p>However, ICH-GCP (E6: Good Clinical Practice: Consolidated Guideline) states that: If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared.</p> <p>It would be advisable that the amended regulation specified if it is acceptable to use an SPC instead of the IB for marketed products being studied for new use (i.e., a new indication).</p> <p>Chapter 3 (21)</p> <p>Further provisions relating to manufacturing: Articles 9-15 "Article 9(2) exempts reconstitution and packaging prior to use from requiring a manufacturing authorisation when it is carried out by specified people, in specified institutions and is for use in such a specified institution. In relation to reconstitution, we interpret the provision as merely clarificatory: reconstitution falls outside the scope of the Clinical Trials regulations and the Directive did not intend to change this. "</p>	<p><u>Template for IB:</u> MHRA will provide guidance on when the SmPC can be used in place of the IB and will provide a mock/example template for the IB on its website.</p> <p><u>Reconstitution of radiopharmaceuticals:</u></p> <p><u>Response:</u> It has been assumed that the radiopharmaceutical is the IMP being tested. 'Manufacture', in relation to an investigational medicinal product, includes any process carried out in the course of making the product, but does not include dissolving or dispensing the product in, or diluting it or mixing it, with other substances used as a vehicle for the purpose of administering it.</p> <p>Any reconstitution would fall outside the scope of this definition.</p> <p>It should be noted that paragraph 5 of schedule 1 to the Medicines for human use (Marketing Authorisation Etc.) Regulations 1994 as amended [SI 1994 3144] cover relevant medicinal products.</p> <p><u>Serious Breach of GCP or protocol:</u> A definition of "serious breach" will be proposed in the Regulations. Guidance will be provided on</p>

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		<p>It has been our recent experience that the Inspectorate of the MHRA requires an IMP manufacturing authorisation to be in place for the reconstitution of radiopharmaceutical kits that takes place in the hospital radiopharmacy. This interpretation of the requirements relating to IMPs is not in line with the situation as it applies to radiopharmaceutical kits which are the subject of a marketing authorisation; under this situation these licensed products are reconstituted in UK radiopharmacies under the practice of pharmacy.</p> <p>In other European countries, an IMP manufacturing authorisation for this process for radiopharmaceutical kits is not needed as the step is covered under pharmacy practice. Therefore to maintain some parity with other countries we request that the MHRA Inspectorate reconsiders this issue and that in the future hospitals are allowed to reconstitute investigational radiopharmaceutical kits without the need for an IMP manufacturing authorisation (similar to situation for marketed products). This would remove the additional administrative burden for the hospitals and resolve the current situation where UK centres are discriminated against compared to those in other countries.</p> <p>Annex 3 Section 2(i) a It would be helpful if further guidance was included</p>	<p>what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p>

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		<p>on potentially ambiguous terms such as "persistent", see below.</p> <p>" (a) To require that MHRA should be notified if a sponsor becomes aware of serious breaches of Good Clinical Practice. Serious' would be where patients safety had been put at risk, persistent non-compliance with protocol and/or GCP, falsification of trials data;"</p> <p>Reply may be made freely available.</p>	
58	<p>Faculty of Pharmaceutical Med 1 St. Andrews Place Regent's Park LONDON NW1 4LB</p>	<p>Chapter 1 Non-Commercial trials – Article 1</p> <p>This Article makes reference to 'specific modalities' or working practices to be introduced for non-commercial clinical trials. Further guidance from the Commission is still awaited. The MHRA particularly mentions these modalities with respect to manufacturing and import requirements and the documentation to be submitted and archived for the trial master file (Chapter 4). In considering what is appropriate, it is vital to ensure that a double standard (commercial vs. non-commercial) does not put trial participants at risk of exposure to poor quality medicines. Similarly, for study documentation (Chapter 4), it is essential that the trial master file permits reconstruction of the trial and a full audit of data prior to publication. Publications of pivotal non-commercial trial data can be extremely influential in changing medical practice. The public health risk of a change in</p>	<p><u>Specific Modalities:</u> The Commission will publish guidance on 'specific modalities' for consultation before finalising.</p> <p><u>Sponsor delegation:</u></p> <p><u>Response:</u> A sponsor could delegate duty to report non-compliance of investigator to an independent person/body but would still remain accountable for ensuring this was done.</p> <p><u>Serious Breach of GCP or protocol:</u> A definition of "serious breach" will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p>

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		<p>practice supported by published data which is not properly verifiable should not be underestimated.</p> <p>Chapter 2 Principles of GCP – Articles 2-5 Further provisions on Ethics Committees – Article 6 No specific comments</p> <p>Sponsor – Article 7 Sponsor/Investigators – The regulations already allow for investigator and sponsor to be the same person. Where there is potential conflict of interest, e.g. sponsor’s obligation to report non-compliance of investigator, there should be a requirement to delegate these sponsor functions to an independent person/body.</p> <p>Investigator’s Brochure – Article 8 The required updates of the Investigator’s Brochure may be an extra burden to non-commercial sponsors, but are of course essential to ensure trial participant safety.</p> <p>Chapter 3 Further provisions relating to manufacturing – Articles 9-15 See comments on Chapter 1. Would encourage the MHRA to be cautious in the implementation of any ‘specific modalities’ for non-commercial sponsors that might impact the quality/documentation pertaining to investigational</p>	

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		<p>medicinal product.</p> <p>Chapter 3 Trial Master File and Archiving – Articles 16-20 See comments on Chapter 1</p> <p>Chapters 5 & 6 Inspections – Articles 21-30 No specific comments</p> <p>Additional requirements Notification of site closure There will be an additional requirement to notify MHRA of serious breaches of GCP. It is recommended that there is both a requirement to notify MHRA of breaches and to terminate participation of the investigator, as notification without termination does not immediately remove the risk to the trial participants. In reviewing the notification, the MHRA may then decide to review the investigator's participation in other ongoing or planned clinical trials.</p> <p>Power to inspect trials without a Clinical Trial Authorisation This proposal is welcomed.</p> <p>Amended procedure for paying fees: This proposal is welcomed</p>	

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59	The Royal College of Radiologists 38 Portland Place LONDON W1B 1JQ	The proposals seems to cover clinical medicine trials and that there are important aspects of good clinical practice which should be adopted in research activity in both of College's specialities of Clinical Radiology and Clinical Oncology. Much of what is covered is already dealt with in recent NHS Research Governance Initiative. Reply may be made freely available.	
60	Dr John Lamberty (Chairman) The Association of Research Ethics Committees Steeping Stones South Staffordshire Healthcare NHS Trust Headquarters Corporation Street STAFFORD ST16 3AG	Overall, the proposed amendments to the regulations seem to be essential to the implementation of the GCP Directive in the UK. The document provides a sound rationale for the proposed changes. It is important that the new requirements placed on EC in relation to document retention and communication (Article 6) with MHRA is clear and implemented. However there are a few points that require clarification:- i) EC are required to retain documents for only 3 yrs, whilst patient records are to be retained for 5 yrs from the end of the clinical trial. This difference may be problematic if there is a need, within subsequent patient litigation proceedings, to obtain evidence relating to compliance with the original intentions and ethical considerations of the study. It may be appropriate to reconcile practices with EC retaining documents for 5 yrs from study completion. However, this may be dealt with in Chapter 4, within the master file and archiving.	<u>Document retention by REC and sponsor/investigator:</u> Retention_times are set by the Directive which cannot be changed at this time. The GCP Directive makes separate provisions for a REC to retain its documents and for a sponsor /investigator to retain the TMF and medical records because it was felt that RECs would not want a sponsor to have access to all of its documents and some aspects of the medical records should not be available to the REC. <u>Communication between RECs and MHRA:</u> This will be described in a written memorandum of understanding and will include an "information gateway" to pass information between RECs and MHRA that will assist them in carrying out their functions. . <u>Sponsor responsibilities:</u> The description is taken from the Commission Q&A document on responsibilities of the sponsor.

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		<p>This could incorporate EC documents into the trial's master file and avoid the EC needing to retain them separately. A single file, retained as the responsibility of the trial co-ordinators, would also be more seamless way of having all evidence to hand.</p> <p>ii) The need to ensure that sponsors remain ultimately responsible for compliance with the Directive even when they delegate trial-related functions to others could be more clearly stated.</p> <p>iii) the term 'medical files' is used throughout. It is not clear whether this includes nursing records.</p> <p>AREC Council supports the proposed amendments and hope that these comments will be useful. Members of the Association Council will be happy to discuss further any of issues raised.</p>	<p><u>Medical records:</u> Does this include nursing records? <u>Response:</u> Only as specified by trial protocols</p>
61	<p>Professor Ian Reid The Royal College of Psychiatrists 17 Belgrave Square LONDON SW1X 8PG</p>	<p>Implementation of the directive would make organizing trails more cumbersome in terms of ethics applications but the major change will be around the administration of the trial documentation which could be quite considerable.</p> <p>This documentation will have to be held by the sponsor (normally a pharmaceutical company) and the clinician usually in case notes which will put additional burden on the medical records functions.</p> <p>No specific comments to make but would like to make a plea for any documentation that is produced as simple as possible</p>	<p><u>Medical Records:</u> There is already a requirement to keep medical records for those involved in clinical trials.</p>

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62	Sara Gray SSL International 1 Old Park Lane Urmston, MANCHESTER M41 7HA	No comments to make on the proposals in MLX 328	
63	Elizabeth Miller Sheffield South West PCT Fulwood Road S10 3TG	No comments to make on the proposals in MLX 328	
64	Mrs Jenny Versnel Asthma UK Summit House 70 Wilson Street LONDON EC2A 2DB	No comments to make on the proposals in MLX 328	
65	Siobhan Miller Royal College of Midwives 15 Mansfield Street LONDON W1G 9NH	<p>The RCM welcomes the extension of the scope of the EC directive to clinical trials held in the UK, since many trials are conducted across EU membership boundaries. The directive will ensure high standards and inter-country consistency. However, the MHRA should continue as national regulator to carry out its legislative duties under UK law.</p> <p>Chapter 1: <i>Non-commercial trials – Article 1, 11. Chapter 1</i> The RCM recommends proceeding with care and welcomes further consultations regarding regulation on ‘specific modalities’.</p>	<p><u>Specific Modalities:</u> The Commission will publish guidance on ‘specific modalities’ for consultation before finalising.</p> <p><u>Retention of documents:</u> Article 17 of Directive 2005/28 Requires retention for at least 5 years or longer where required by other applicable requirements.</p>

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		<p>Chapter 2 <i>Article 6</i> – further provisions of ethics committees RCM welcome the tightening of the role of external assessors.</p> <p>Chapter 4 <i>Retention of medical records</i> RCM support the notion that consideration be given to the inclusion of ‘specific modalities’ referred to in Article 1. further consideration should be given to retaining subjects’ medical records for longer than the recommended minimum of 5 yrs, depending on the nature of the trial and the level of drug interaction in the body.</p> <p>Chapter 5 & 6 <i>Arrangements for paying MHRA application fee-amendment procedure for paying fees</i> Any amendment should ensure that trials are not permitted to proceed until fees have been processed, i.e. money should be paid up front before the trials proceed.</p> <p><i>Notification of site closure</i> The RCM supports these provisions, although they have reservations about the potential influence of sponsors who have the double role of investigator.</p>	

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66	Andrew Matthews Community Health Council c/o Carmarthen CHC 103 Lammas Street CARMARTHEN SA31 3AP	<p>The MHRA's Clinical Trials Regulations 2004 SI 2004/1031 which came into force 1 May, must be one of the strictest set of regulations in the world, however, failures occur in clinical trials for medicines for human use, especially in the protection of patients used in trials.</p> <p>Many trials in the Pharmaceutical Industry and Sponsored section are cross-border and need to be controlled by common regulations and directives. The EC must ensure the regulations and directives apply to all European Countries, including new member states. This must finally lead to international standards, although this may be difficult to control. Many international companies undertake studies in the poorest developing countries where patient rights are non-existent and where records are badly kept.</p> <p>Cost estimates show no increase in most aspects of the new directives, but small companies estimate costs will increase and their clinical trials may be reduced. Will the EC support these companies?</p> <p>Why does the Directives and Regulations have lesser effect on the control on trials and manufacturing of generic drugs? Generic drugs are being used more and more by all hospitals and GPs in the UK because of the cost benefits. Many drugs are manufactured in the developing countries such as Bangladesh. Will the new</p>	<p><u>Cost estimates:</u> The consultation document sought specific information about increased costs.</p> <p><u>Controls on Generic Medicines:</u> The regulations will require a high standard of quality assurance and quality control for IMPs that are generic products.</p> <p><u>Specific Modalities:</u> The Commission will publish guidance on 'specific modalities' for consultation before finalising.</p> <p><u>Options for Serious Breach of GCP or protocol:</u> Supports sponsor terminating investigator contract.</p>

Item	Organisation	Summary of reply	MHRA Comments
		<p>Directives have stricter control on the importation and testing of these drugs?</p> <p>MHRA inspection procedures are in line with the requirements of the GCP Directive but some of the procedures are not on a statutory basis, it is therefore essential the higher standards are achieved by the implementation of GCP directives.</p> <p>Chapter 1: Specific provisions for non-commercial trials</p> <p>The Board supports the Commissions intention to prepare guidance on specific ways of working which can be applied to certain non-commercial trials. It further supports the intention to consult stakeholders and take account of comments before finalising the guidance. The Board would appreciate a copy of the final guidance when it is available.</p> <p>Chapter 2: Principles of Good Clinical Practice</p> <p>The Board supports:</p> <ul style="list-style-type: none"> • The requirement for ethics committees to retain documents for at least 3 yrs. • The view that sponsors may delegate aspects of clinical trials but still retain overall responsibility. • The proposal for an investigators brochure, which is concise, simple and objective, balanced and non-promotional. 	

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		<p>Chapter 4: Trial Master File & Archiving The supports the amendment specifying retention of medical records for a minimum of 5 years post trial.</p> <p>Chapter 5 & 6: Inspections – Articles 21-30 The Board supports MHRA new rules which inspectors must follow.</p> <p>Additional requirements – comments</p> <ol style="list-style-type: none"> 1. Reg 30 – strongly support sponsors terminate investigators contract when patients’ safety is put at risk, non-compliance with protocol or falsification of trial data. 2. Reg17b(ii) – support the amendment to allow guaranteed fee payment for trial to follow request for authorisation. <p>Finally, although there are some areas to be fully defined, the Option 2 would appear to be the most suitable preference. Careful monitoring of the new Procedures will be essential to prevent any further disasters in the prescribing of Medicines for Human Use.</p>	
67	<p>Professor Shuagh O’Brien Vice-President, Standards Royal College of Obstetricians & Gynaecologists 26 Sussex Place, Regents Park LONDON NW1 4RG</p>	<p>In principle, the new requirements for sponsors/ Investigators seem appropriate and in line with modern good clinical practice. Harmonisation is particularly helpful as collaboration from UK institutions with EU sites and centres increases, eg multicentre, international randomisation controlled trials requiring identical terminology, standards and</p>	<p><u>Costs of implementation:</u> The consultation sought specific information on increased costs resulting from implementing these amendments.</p>

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		<p>practice. It would be important for the regulatory inspectors to receive appropriate training, support and education for the revised system to work efficiently. The implementation costs do not appear to be clearly thought through and will need fleshing out.</p> <p>It is felt that the regulation will add further to the large burden of paperwork involved in conducting clinical trials.</p> <p>However, the following concerns are raised about the content of the Partial Regulatory Impact Assessment (Annex 3), which underpins the recommendations.</p> <p>1. Item 2(iii) – Risk Assessment</p> <p><i>Risk to clinical trial subjects: paras4/5:</i> These two paragraphs seem disingenuous. The MRHA should have statistics on potential for risk to patients included in current clinical trials using critical incident reporting, which is now well embedded within the risk management systems of hospital trusts. The examples given are not well documented and appear somewhat unconvincing. As far as they are aware there is no evidence that “medication errors” occur equally frequently in clinical trials as in normal medical practice. In their experience, patients involved in clinical trials have higher level input, with more medical and nursing time spent on them, hence one</p>	<p><u>RIA, Risk assessment:</u></p> <p><u>Response:</u> There have been about 14 GCP whistleblower cases in the last 12 months. About 10 inspections have been carried out in relation to these. Where minimal work is required by MHRA, no fee is charged. Where justified by work involved, a full fee of £15,000 (05/06 rates) has been charged. Whistle blowing procedures are being kept up to date.</p> <p><u>Cost and bureaucracy:</u> Information is being sought on additional costs for small academically led trials.</p>

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		<p>Would expect a lower level of errors. The MHRA should obtain data to support this assertion.</p> <p><i>Risk to public health:</i> The risk assessment identifies the problem of possible fraud but it is not stated clearly how the new regulations will reduce the chance of fraud – will the “clever cheats” easily circumvent the new regulations? It would be important that the regulatory inspections have the power to observe, assess, intervene and ultimately to withdraw permission to continue research project if violation is proven.</p> <p>2. Item 8 – Results of consultations</p> <p>The section mentions concerns by the MRC and others involved in publicly funded trials that arose in the February 2003 consultation on clinical trial regulation. A joint project was taken forward but the MHRA agrees that they have been able to accommodate only some of the concerns raised by the academic research community.</p> <p>The system of research supervision and governance should be able to tell the difference between multi-million dollar trial of a new class of chemotherapy with potentially life-threatening side effects and a small scale low risk comparison of two widely used generic products, for example. At present no such differentiation exists and the bureaucratic burden is excessive.</p>	

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68	Claire Lowe British Dental Association 2 Caspian Point Cardiff Bay CARDIFF CF10 4DQ	<p>The BDA is pleased to have been given the opportunity to comment on this consultation document. The proposals outlined seem reasonable and we are pleased to note that there will be no amendment to the regulations concerning the repackaging of medicines in hospitals and health centres for use in clinical trials (Chapter 3).</p> <p>The BDA would also like to point out a very small error on page 2 of the document. In paragraph 2, line 1 the "l" is missing from "health centres". Trust these comments are useful. "Chapter 3 Manufacturing Exemption for hospital and health centres and reconstitution: The Regulations already state that a hospital or health centre does not need to hold a manufacturing" Reply may be made freely available.</p>	
69	Maxine Stead UK Clinical Research Network Arthington House Hospital Lane LEEDS LS16 6QB	<p>This response is being sent on behalf of the UK Clinical Research Network.</p> <p>Although UKCRN recognise that the principles of good clinical practice in Directive 2005/28/EC and those in the Clinical Trials Regulations, 2004, are very similar, they believe that it will cause confusion to the research community to change them. The proposed amendments replace the list of principles based on the ICH guidelines, which is the international standard agreed by Europe, the</p>	<p><u>Principles of GCP:</u> UKCRN concerned that changing wording from ICH GCP guideline will cause confusion without benefits. Commission lawyers advised that ICH wording could not be used.</p> <p><u>Specific Modalities:</u> The Commission will publish guidance on 'specific modalities' for consultation before finalising.</p> <p><u>Trial Master File:</u> Commission to publish guidance on content of TMF.</p>

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		<p>USA and Japan. The change in Directive 2005/28/EC may give the impression that Europe no longer upholds those standards.</p> <p>The UKCRN note that the guidance on “specific modalities” is currently being prepared by the Commission and UKCRN would welcome the opportunity to comment on the draft guidance before it is finalised.</p> <p>The UKCRN welcome the potential flexibility implied in Article 16, Chapter 4 whereby the content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial and await the Commission guidance on the content of the Trial Master File. This should not only reflect the phase of the clinical trial, but also the specific modalities as described in Directive 2005/28/EC.</p> <p>Reply may be made freely available</p>	
70	<p>The Institute of Clinical Research Thames House Mere Park, Dedmere Road Marlow, BUCKS SL7 1PB</p>	<p>It is essential a comprehensive definition of serious breach of GCP is included in the legislation (or supporting guidelines issued at the same time) to avoid the risk of inconsistent interpretation. It strongly encourages the adoption of notification system a). It would be useful if the legislation or supporting guideline indicated the consequences of notification e.g. MHRA for cause audit of the site</p> <p>Modalities for Academic Trials:</p> <p>It understand that delays in Commission guidance result in the uncertainty regarding modalities for</p>	<p><u>Serious Breach of GCP or protocol:</u> A definition of “serious breach” will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p> <p><u>Specific Modalities:</u> The Commission will publish guidance on ‘specific modalities’ for consultation before finalising.</p>

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		<p>academic trials; as modification of the UK legislation is expected anyway following Commission guidance it would be better to take a less ambiguous position in the UK legislation now.</p> <p>Infringement notice It would be useful to indicate possible consequences of an infringement notice.</p> <p>Archiving: Experience proves that Principal investigators often shirk the activity of archiving patients medical and site trial records. Encourage the legislation to be enhanced by not only stating a requirement for 5 years retention of records but that the Principal Investigator is responsible for this (regarding site related documents).</p> <p>Exemption from QP Release for IMP: This is not specifically addressed in this document. It requests that the authority consider adding detail on this in the legislation (or a guidance document), in particular addressing the relationships between institutions that would allow qualification for exemption. Reply may be made freely available.</p>	<p><u>Infringement Notice:</u> Can MHRA provide guidance on the consequences of receiving an infringement notice? <u>Response:</u> There are not direct consequences of receiving an infringement notice. It serves as a means for the sponsor and the inspectorate to encourage compliance without invoking a criminal prosecution. The GCP inspectorate have too little experience to know whether or not they will be effective.</p> <p><u>Record Retention by principle investigator:</u> <u>Response:</u> It would be sensible to make the chief investigator responsible for retaining investigator site essential documents, including source records; provision has been made for this.</p> <p><u>Exemption from QP release:</u> <u>Response:</u> Regulation 37 of the CT Regulations provides an exemption from the need for a hospital or health centre to hold a manufacturing authorisation to assemble an IMP in a hospital or health centre, when the "assembly" is carried out by a doctor or pharmacist, or under the supervision of a pharmacist. "Assembly" is related to packaging and labelling, and not to the preparation of medicines from their ingredients. The exemption applies only if the product is to be used exclusively in that</p>

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			hospital or health centre or any other that is a trial site for the clinical trial in which the product is to be used. There is no specific exemption for a QP
71	<p>Dr Colin Wilsher GCP Committee Chairman British Association of Research Quality Assurance 3 Wherry Lane Ipswich SUFFOLK IP4 1LG</p>	<p>The committee thanks the MHRA for the opportunity to provide comments.</p> <p>Non-Commercial Trials: Article 1</p> <p>With regard to specific modalities, the suggestion that commercial and non-commercial trials will have different standards with regard to implementation of GCP is very concerning. As a professional society of auditors we feel that it is very important that a single and high quality standard for GCP be adopted.</p> <p><i>Trial Master File and Archiving: Articles 16-20</i></p> <p>Comments:-</p> <p>The paragraph starts with a requirement for “Sponsors & investigators” but in fact it may be referring to only the <i>Investigators’</i> “subject’s medical files”? Presumably this is different to the requirement under 2001/83/EC and 2003/63/EC for the Sponsor to retain essential documents for a longer period? It is also a different requirement from that of ICH GCP and may lead to a lowering of standards and possible confusion between the internationally accepted guideline (ICH GCP) and UK requirements.</p>	<p><u>Specific Modalities:</u> The Commission will publish guidance on ‘specific modalities’ for consultation before finalising.</p> <p><u>Medical Records: Response:</u> It would be sensible to make the chief investigator responsible for retaining investigator site essential documents, including source records; provision has been made for this.</p> <p><u>Serious Breach of GCP or protocol:</u></p> <p>A definition of “serious breach” will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p>

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		<p>Additional Requirements. Notification of site closure 28.</p> <p>Comments:-</p> <p>There were serious concerns about this section. The GCP Committee were unclear about how options “a” and “b” would operate. If new regulation is required, it should be based upon a known event, such as the closure of a site or removal of investigators by the sponsor. The procedure for Regulation 24 should adopted not Regulation 30. The definitions of “Serious breaches of GCP” offered in Paragraph 28 are inadequate, as they are too open to interpretation. For instance it gives an example of “persistent non-compliance” but does not define what level of non-compliance (seriousness); over what period; and what detail is expected with regard to efforts to correct the problem (persistence). Equally with regard to patient safety, more detail on what constitutes “being put at risk” is needed. Hopefully this excludes remote potential hazards and has some way of being able to measure the degree of risk and the seriousness of a possible outcome should the threat materialise. It is suggested that the following as more workable examples:</p> <ul style="list-style-type: none"> • Scientific misconduct or fraud • Professional negligence directly related to 	

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		<p>patient care</p> <ul style="list-style-type: none"> • Patient's safety put at risk, e.g. actual harm to the patient, or where there is imminent potential for direct effect on patient safety. <p>There is no detail on the duties of those, other than the Sponsor, who discover non-compliance. Reply may be made freely available.</p>	
72	<p>Dr Gordon Birnie Hayfield House Hayfield Road Kirkcaldy FIFE KY2 5AH</p>	<p>NHS Fife Operational Division welcomes the opportunity to respond to the Medicines and Healthcare Regulatory Agency consultation on revisions to the Clinical Trials Regulations to implement the European Commission's Directive on Good Clinical Practice (2005/28/EC). Whilst supporting the Directives efforts to improve research standards by bringing existing good clinical practice guidance into legislation, there would be concerns about increased cost implications for publicly-funded research which might result. Under Specific provisions for non-commercial trials we note that the Commission is currently preparing guidance on specific ways of working which may offer some flexibility for certain non-commercial trials.</p>	<p><u>Cost and bureaucracy:</u> The consultation sought specific information on increased costs resulting from implementing these amendments including additional costs for small academically led trials.</p>
73	<p>Dr Christiane Abouzeid Regulatory Affairs Manager BioIndustry Association 14-15 Belgrave Square LONDON SW1X 8PS</p>	<p><u>Chapter 2: Investigator's Brochure</u> BIA recognizes that the requirements of the investigator's brochure as specified in Article 8 need to be implemented. However they do not concur with the MHRA proposal to implement Article 8(3) with the <i>additional requirement that the</i></p>	<p><u>Investigator Brochure update:</u> Clinical trial sponsors should <u>review</u> Investigator Brochures at least annually. The IBs may not require updating, but they should at least be reviewed annually where there is on-going trial activity (either trials sponsored by the sponsor</p>

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		<p><i>Investigator's Brochure</i> be updated in response to specific emergent safety concerns, as this goes beyond the scope of the Directive.</p> <p>Directive 2001/20/EC was introduced to facilitate harmonisation of laws and regulations relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products supplemented by the further provisions in Directive 2005/28/EC in order to achieve optimum protection of health. BIA would hope that, when implementing the Directive into national law, Member States would limit the inclusion of additional requirements into local statutory regulations, thereby minimising a move away from the harmonised approach that industry seeks in the European Union.</p> <p>BIA urge the MHRA to keep the current approach of issuing 'safety letters'. They believe that this is a practical and acceptable approach in the response to and notification of specific emergent safety concerns, and therefore do not see the necessity for this additional requirement to form part of the legal provisions implementing the Directive. This new safety information would subsequently be incorporated into the Investigator's Brochure at the time of update.</p> <p>BIA believe that the MHRA proposal to update <i>the Investigator's Brochure in response to specific emergent safety concerns</i> has the potential to</p>	<p>organisation or investigator-initiated trials that the sponsor has been notified of). This is currently routine practice in the commercial sector. The IB should be updated more frequently, if significant new safety information becomes available that may have an impact on the evaluation of risk/benefit. This information may come from pre-clinical or clinical trials, but where the investigational product is marketed (in any territory), the information may also come from the use of the product in routine clinical practice</p> <p><u>Format of 'Statement of Manufacturing Process:</u> The proposed amendment to the regulations requires a 'statement of the manufacturing process where an application relates to inactivation of viral or non-conventional agents. It is envisaged that this obligation can in most cases be satisfied with a copy of the information provided in the IMPD of an application for a CTA. In some cases more detailed information may be required to allow assessors to determine whether any particular issues relating to GMP have been considered e.g. viral inactivation studies.</p> <p><u>Content of TMF:</u> The Commission will provide Guidance on this with the consensus of the Member States.</p>

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		<p>delay the dissemination of information to the concerned parties.</p> <p>If this approach is adopted solely by the UK, this will require a different approach to updating concerned parties of emergent safety concerns in an international multi-centre clinical trial.</p> <p>Moreover, they would suggest that the requirement for annual updates applies only where there are ongoing clinical studies to avoid any unnecessary burden, as there may be periods when companies are awaiting further funding or in negotiations with regulatory authorities.</p> <p>Chapter 3: Manufacturing/Import Authorisation</p> <p>Article 9 (1): Definition of partial manufacture</p> <p>The BIA would like to ask the MHRA to request the European Commission to explain the meaning of partial manufacture of investigational medicinal products.</p> <p>BIA would welcome clarification on the definition of partially manufactured products as this is causing our member companies some business issues, in particular contract manufacturers. What characterises a partially manufactured product? At which stage of the manufacturing process do we have partial manufacture? Will a manufacturing or import authorisation be required for an intermediate product?</p>	<p><u>Serious Breaches of GCP:</u> Are the provisions of Reg 29 and Reg 30 sufficient to allow reporting of Serious Breaches of GCP? If not option 1 preferred. A definition of “serious breach” will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p> <p><u>Response:</u> They are not sufficient as they do not require reporting to MHRA when compliance is breached in an unapproved way when not required as an urgent safety measure.</p>

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		<p>Article 10(1) (c):requiring the applicant to specify the manufacturing process where relevant</p> <p>Currently, details of the manufacturing process are covered in the IMPD, which forms part of the Clinical Trial Authorisation. In order to ease this additional burden on applicants, we would recommend that the information for the Manufacturing Authorisation Application be presented in the same format as required for the IMPD.</p> <p><u>Chapter 4: Trial Master File and Essential Documents</u></p> <p>It is our view that the content of these documents should be specified through guidance rather than regulation, in particular the awaited Commission's detailed guidance. This should also tie in with the ICH E6 requirements for Essential Documents.</p> <p>Additional Requirements</p> <p>Notification of Site Closure - Serious Breaches of GCP</p> <p>Directive 2001/20/EC and the Commission guidelines provide that the sponsor takes responsibility for the conduct of the clinical trial. Sponsors are already required to notify the MHRA of all site closures either under Regulation 30 (Urgent safety measures) or Regulation 29 (Conduct of a clinical trial in accordance with</p>	

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		<p>clinical trial authorization, etc).</p> <p>We believe that the current provisions would be sufficient, as they would capture all site closures irrespective of the reason for closure. However, if the MHRA intends to create a requirement for sponsors to notify the Agency when they become aware of serious breaches of GCP, then the first proposal of introducing a simple requirement is the preferred approach.</p>	
74	<p>Dr C.P. Swainson Medical Director NHS Lothian Deaconess House 148 Pleasance EDINBURGH EH8 9RS</p>	<p>NHS Lothian welcomes consultation on implementation of the EC Directive on GCP. It is also appreciated that much of the consultation document provides a welcome clarification rather than introducing new regulatory requirements and look forward to more detailed guidance on “specific modalities” which will be applied to non-commercial studies. The impact of this guidance is therefore uncertain.</p> <p>NHS Lothian believes that the new required contents of the Investigator’s Brochure and a Trial Master File will be beyond the adhering to the principles of Good Medical Practice. Both Universities and the NHS are still effecting a substantial cultural change in their roles as academic sponsors. New administrative requirements require investment in both people and resources, and they have already established a clinical trial organisation to provide a means of ensuring that trials which they sponsor are co-</p>	<p><u>Investigator Brochure update:</u> (see response to item 73)</p> <p><u>Inspection of trials not holding a CTA:</u> <u>Response:</u> Essentially, if a trial is running without approvals (when it should have them) we would inspect to establish that it was a clinical trial that was current and require that the trial was suspended until all necessary approvals had been obtained.</p> <p><u>Data Verification: Response:</u> It would be negligent, and possibly dangerous, to produce a clinical trial report without having verified that the supporting data were reliable.</p>

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		<p>ordinated and managed in line with ICH GCP. There is likely to be a major impact for full implementation of more detailed administrative requirements proposed in this consultation for non-commercial studies. Delegation is not the only answer as this may simply shift costs from one sponsor to another.</p> <p>The proposal to give MHRA powers to inspect studies not holding a CTA would need to be described in more detail as to how this fitted within the existing MHRA remit. This could be interpreted as giving MHRA the authority to inspect any clinical study on the chance that it might turn out to be a clinical trial.</p> <p>NHS Lothian also welcomes the specified minimum period for archiving medical notes and essential documents. NHS Lothian would also welcome further explanation of the responsibility outlined for sponsors in respect of “to verify data” prior to publication. This could be interpreted as requiring non-commercial sponsors to undertake source data verification. While NHS Lothian is implementing a system of trial audit, they are following the MRC Department of Health Joint Working Group Advice that audit is proportionate to the risk proposed by the trial. For low risk studies they do not anticipate audit involving source data verification.</p>	

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75	<p>Dr. Joanna Nakielny Medical Director Eli Lilly and Company Limited Lilly House Priestley Road Basingstoke</p>	<p><i>Ethics Committees</i> Lilly UK are assuming that for Clinical Trials with Investigational Medicinal Product, the proposal for Ethics Committees to retain documents for at least three years would be three years from the end of the Clinical Trial. We would question whether this would be a sufficient period considering the length of time the Sponsor is required to retain essential documents relating to a Clinical trial and would suggest that the period was extended to a minimum of 5 years.</p> <p><i>Chapter 3 Principles Manufacturing</i> <u>Exemption for hospital and health centres and reconstitution</u> Lilly would welcome confirmation that the exemptions detailed in Article 9(2) apply to pharmacies located within phase I CROs, as well as hospital and health centre pharmacies. Further, Lilly would request that phase I CRO pharmacies are treated in the same manner as hospital pharmacies and therefore are not required to have GMP authorisation for dispensing and relabelling operations. The role undertaken in phase I CROs equates to the role undertaken by hospital pharmacies for these activities. The current understanding by the phase I CROs in the UK is that they need to have GMP authorisation and thus access to a Qualified Person. This is a significant burden for the phase I CRO and the sponsor.</p>	<p><u>Retention of records by RECs:</u> The period is at least three years after the completion of the trial. This will be made explicit in the amended regulations</p> <p><u>Retention of documents:</u> Article 17 of Directive 2005/28 Requires retention for at least 5 years or longer where required by other applicable requirements.</p> <p><u>Exemption for hospital and health centres and Reconstitution:</u> the Regulations already provide that a hospital or health centre does not need to hold a manufacturing authorisation for the packaging and labelling of medicinal products for use in a clinical trial. For the exemption to apply the activity must be carried out by specified people and the repackaged or labelled medicinal product is to be used exclusively in that hospital or health centre or any other that is a trial site for that clinical trial in which the medicinal product is to be used. Reconstitution of a medicinal product for use in a clinical trial does not fall within the scope of manufacture. We do not propose any amendment to this aspect of the Regulations.</p> <p><u>Serious Breach of GCP or protocol:</u> A definition of “serious breach” will be proposed in the Regulations. Guidance will be provided on what is considered to be a serious breach of</p>

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		<p>Chapter 4 Trial Master File <u>Retention of medical records</u> The proposal indicates a minimum of five years as the retention period for a trial subject's medical files. However the Directive 2005/28/EC states that they should be retained in accordance with the maximum period of time permitted by the hospital, institution or clinic. Therefore the hospital's policy could conflict with the proposed retention time. In addition, we would question whether five years would be a sufficient period considering that the trial subject's medical files would be required in the event of an inspection of that trial site.</p> <p>Additional Amendments <u>Serious breaches of GCP</u> Of the two options suggested in the proposal, Lilly UK would prefer to have an introduction of the requirement to notify the MHRA when we become aware of serious breaches of GCP, rather than be obligated to terminate the participation of the responsible parties. However, if this option is implemented we feel that it would be useful guidance could be developed on the serious breaches that would require reporting to the MHRA, to help ensure consistency in reporting and to help prevent over/under reporting in this area due to interpretation of the term 'serious'.</p>	<p>GCP with examples Serious includes non-compliance with GCP conditions and principles set out in Schedule 1. (see response to item 39)</p>

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76	Dr Ela Shah E-mail: eladevishah@aol.com 50 Elmcroft Crescent London NW11 9SY	I agree on proposal for the good clinical practice to be implemented of 2001 and 2004. Why not include the consideration of avoiding potential skin sensitizers in moisturizers in the good clinical practice? How many patients suffer from hypersensitivity due to prescription of diprobase and dalacin C containing chlorocresol and cetosteryl alchohol. Why sudo pred is so much prescribed to children? Do you get complaints yellow cards or not? I am writing What I have identified and feeling for safety of the public. My reply may be made freely available	The MHRA consider the safety aspects of all trials including those of skin preparations and medicines for children both before the trial is commenced and during its conduct.