

Review of Provisions given by Research Ethics Committees

Introduction

The HRA Business plan 2016-2017 included a commitment from the Research Ethics Service to continue to provide an efficient, responsive, proportionate, effective and robust Research Ethics Committee operation. One of the programme areas prioritised was the improvement in consistency of decision making. The related aim was to reduce the number of Provisional Opinions at first review to strengthen confidence in the expected timelines for decisions, minimising duplication of review. The provisional opinion rate was to be measured as a key performance indicator by the HRA Board.

A review of provisional opinions was undertaken to show the commonality of the provisions given by REC.

Review Aims

- To highlight any provision trends associated with particular IRAS study or sponsor types.
- To consider the communication routes and relationships the HRA currently have in place with the sponsor types.
- To offer suggestions for the feeding back of learning points to sponsors to increase the quality of submissions.
- To highlight opportunities for improving the consistency of REC practice and administration.

The Analysis

- The review covered a 6 month period (1/10/15- 31/03/16).
- The review included full REC and Proportionate Review data from across the UK.
- The data was first divided by study type and then by lead sponsor type.
- Five provisional opinion letters per study type and lead sponsor type were reviewed and categorised in line with the provisional opinion audit plan. The submission of Research Tissue Banks and databases is voluntary in the UK and will not be included in the review.
- Each point within the provisional opinion letters was coded in line with the provisional opinion review codes (detailed below). I.E. if the letter included 6 requests for minor clarifications it was reported as 6x5.2 in the review.

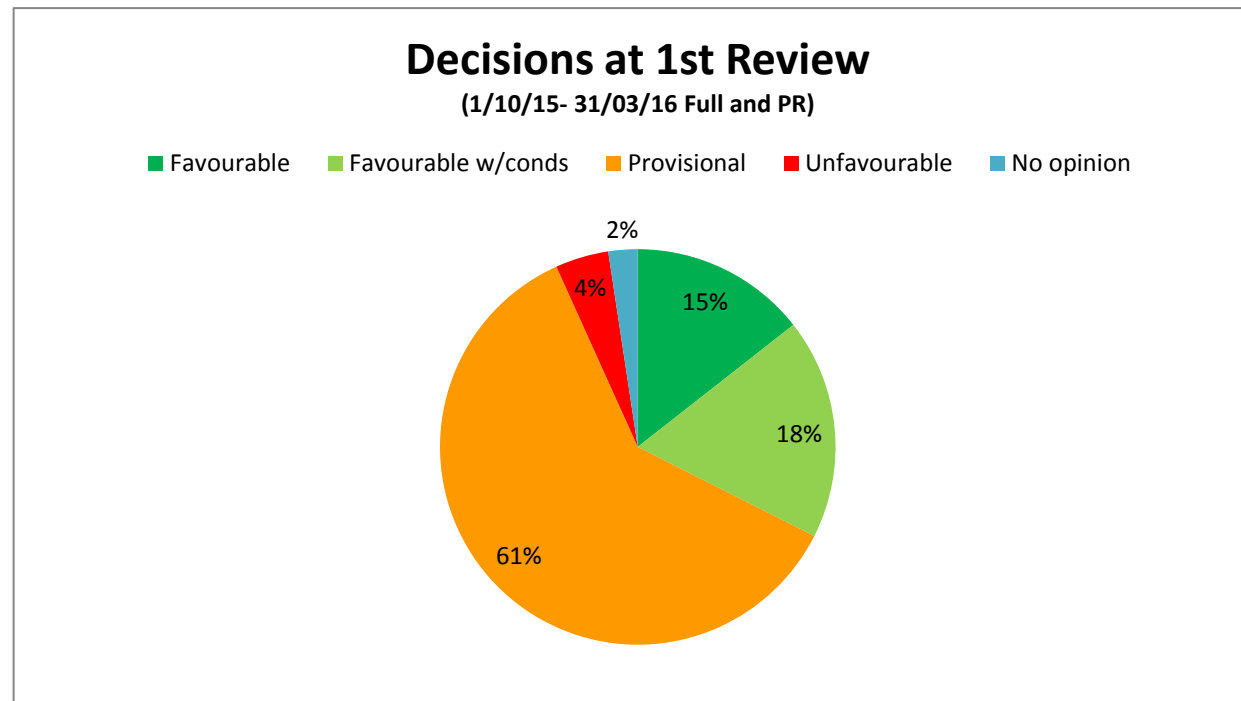
Provision Category	Example	Code
Substantial Changes to the Information Sheet/Consent Form/Invitation Letter	Complete re-write of the information sheet, request to add further study specific information/paragraphs	1.1
Minor Changes to the Information Sheet/Consent Form/Invitation Letter	Administrative changes, changes to formatting, addition of standard paragraphs specified in guidance, addition of complaints contact details, addition of hospital header.	1.2
Provide/ Produce new participant facing documentation or documentation which will be used with the participant.	New information sheet/ consent form for participant group, new advertising material, questionnaires, topic guides.	2.1
Provide/produce/revise documentation which is not participant facing .	Insurance certificates, minimally revised IRAS form, GP letter , Investigator CV.	2.2
Substantial changes to the protocol	Request to re-consider/change study design, request to omit stated procedures, request to add a procedure not currently in the protocol.	3.1
Minor changes to the protocol	Clarifications about participant numbers	3.2
Reconsider/Change proposed participant group inclusion/exclusion criteria	Omit MCA, omit children, include patients with	4.1
Request for clarifications (significant) ¹	Clarifications about the recruitment strategy, level of access to patient notes, storage of identifiable data, use of a drug, use of a participant group, use of a procedure	5.1
Request for clarifications (minor)	Clarifications about participant numbers, inconsistencies in the information between the documentation.	5.2
Other	E.g. Issues not picked up at validation stage, which require significant changes to the IRAS form (radiation, categorisation). Request for researchers to attend GCP training, request to pay expenses.	6.1

Note1. In relation to code 5.1 the term 'significant' refers to the ethical importance of the clarification not the quantity of clarifications required.

Overview of Management Information (MI) data

-3052 applications were reviewed and issued a decision at first review between 1/10/15- 31/03/16.

-1856 applications (61%) were give a a provisional opinion at first review.



Audit Findings

Commonality of Provisions Across All Study Types

The most common provisions requested minor changes to the information sheet and requests for clarifications (significant) .

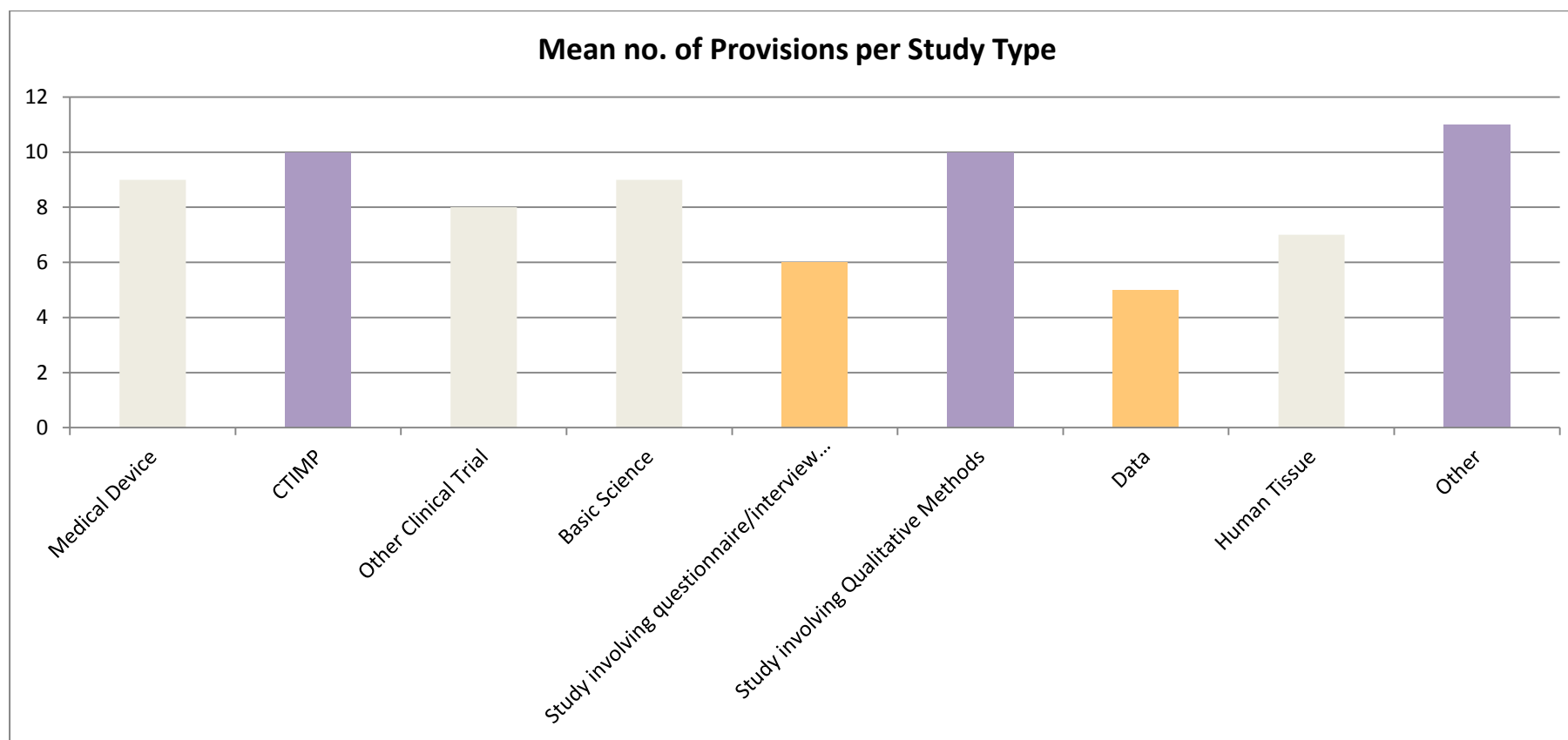
The least common provisions involved requests to amend the participant group and minor changes to the protocol.

Provision Code	% of Provisions Across All Study Types Combined.
1.1 Substantial Changes to the Information Sheet/Consent Form/Invitation letter	9%
1.2 Minor Changes to the Information Sheet/Consent Form	53%
2.1 Provide/ Produce new participant facing documentation or documentation which will be used with the participant.	5%
2.2 Provide/produce/revise documentation which is not participant facing .	4%
3.1 Substantial changes to the protocol	2%
3.2 Minor changes to the protocol	1%
4.1 Reconsider/Change proposed participant group inclusion/exclusion criteria	0.50%
5.1 Request for clarifications (significant)	16%
5.2 Request for clarifications (minor)	6%
6.1 Other	3%

Mean Number of Provisions Per Study Type

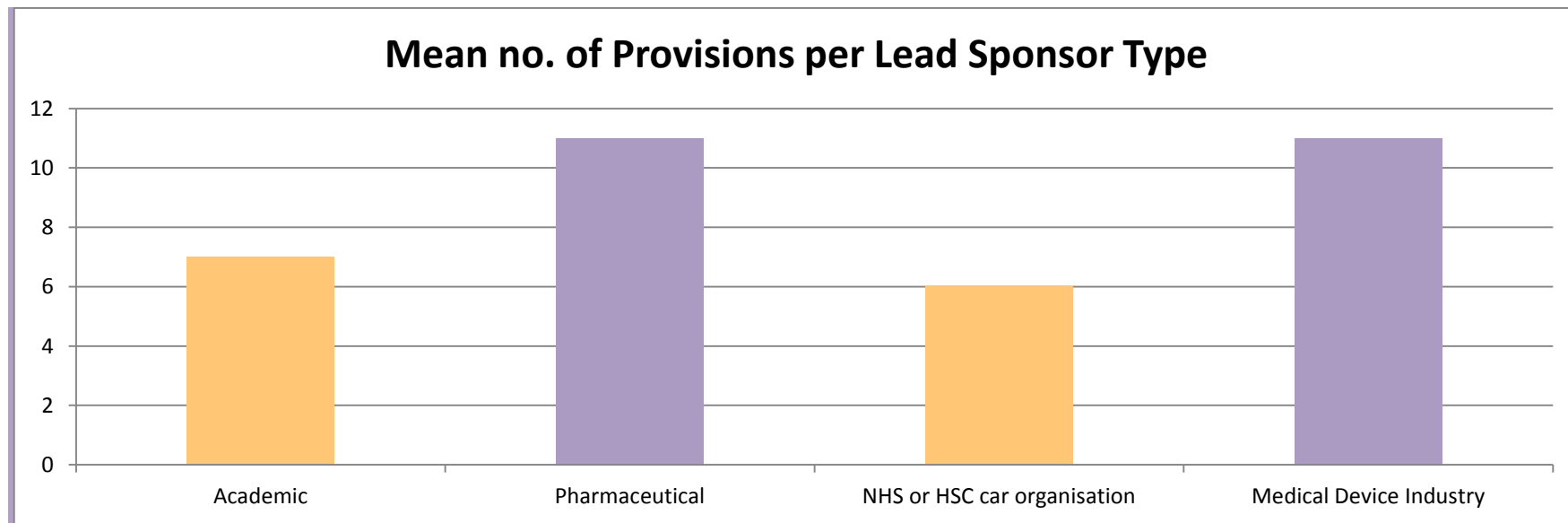
The review indicated that a higher number of provisions were given to ‘Other’ studies, ‘CTIMPS’ and ‘Studies involving qualitative methods only.’

The fewest number of provisions were given for 'Study limited to working with data (specific project only)' and 'Study administering questionnaires/interviews for quantitative analysis or using mixed quantitative/qualitative methodology'.



Mean Number of Provisions per Sponsor Type

The sample reviewed showed that the highest number of provisions were given to the applications sponsored by the Pharmaceutical and Medical Device Industry. This may however be associated to the complexity and level of perceived risk involved in clinical trials sponsored by the such industries rather than a reflection on the quality of the submissions.



Overview of Provisions

Clinical Investigations or other studies of medical devices

1.0. Provision themes : All sponsor types

- Participant Information Sheets did not include sufficient information about the study procedures, what is additional to standard clinical care (if applicable) and what is required of participants.
- Submissions did not adequately detail the process should study procedures gave rise to incidental findings of clinical significance.
- Participants information sheets and consent forms were geared towards one cohort. Frequent requirement to submit further documentation.

1.1. Provision themes: Academic Lead Sponsor

- Insufficient detail about the procedure if a participant becomes distressed.
- Requirement for further information about the recruitment process.
- Omission of advertising materials.

1.2. Provision themes: Medical Device Lead Sponsor

- Assumed knowledge about how the device works. Requirement for further information to be added to the informatio sheets.
- No detail included in the PIS about the risk attached to radiation (when research involved exposure).
- Requirement to re-consider the recruitment strategy and to ensure there is no selection bias.

1.3. Provision themes: NHS or HSC Care Organisation Lead Sponsor

- Research summary (A6-1) does not accurately reflect the purpose of the research.

Clinical Trials of Investigational Medicinal Products

2.0. Provision themes : All sponsor types

- Limited/no information about the provision of the study drug post trial.
- Insufficient detail about the data monitoring Committee, it's membership and affiliation.
- Not clear in the participant information sheet which procedures form part of standard clinical care and which are study driven.
- Not explicitly detailed in the information sheets when standard clinical treatment/medication are to be withheld.
- Emergency contact details omitted within the PIS.

2.1. Provision themes: Academic Lead Sponsor

- Insufficient information about data safety, handling, storage and destruction.

2.2. Provision themes:Phrmaceutical Lead Sponsor

- Unclear how it would be handled if there were findings of clinical significance.
- No distress policy.
- Not clear in PIS how the substance has previously been used.
- Side-effects frequency is not clear in the participant information sheets.
- Summary information sheets have not been produced/submitted (though not always required).

2.3. Provision themes: NHS or HSC Care Organisation Lead Sponsor

- No information about the complaints contacts/process.

Other clinical trials to study a novel intervention or randomised clinical trial to compare interventions in clinical practice

3.0. Provision themes : All sponsor types

- Distress policy unclear.
- Insufficient documentation- participant information sheets and consent forms geared towards one cohort only.
- Limited information about the feeding back of incidental findings of clinical significance to participants and their clinicians.
- Not enough information about data handling, anonymisation and transfer.

3.1. Provision themes: Academic Lead Sponsor

- No complaints details/procedure within the participant information sheet.

3.2.Provision themes:Phrmaceutical Lead Sponsor

- Insufficient information about the storage, handling and transfer of samples.
- Limited information about the anonymisation of data and confidentiality arrangements.

3.3 Provision themes: NHS or HSC Care Organisation Lead Sponsor

- Insufficient information in PIS about what the study procedures entail.

Studies administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology

4.0. Provision themes : All sponsor types

- Distress policy unstated or not clear.
- No strategy for dealing with disclosed, sensitive information..
- Insufficient detail about the anonymisation of confidential data.
- Insufficient information about the process for the identification of potential participants.
- Requirement for further detail about the anonymisation and handling of sensitive, personal information

4.1. Provision themes: Academic Lead Sponsor

- No emergency contact details provided in the PIS.

4.2. Provision themes: Pharmaceutical Lead Sponsor

- Consideration has not been given to how to make study results available to participants.

4.3. Provision themes: NHS or HSC Care Organisation Lead Sponsor

- No complaints contact or procedure on the participant information sheets.
- It is not planned to make results available on a publicly accessible database.

Studies involving qualitative methods only

5.0 . Provision themes : All sponsor types

- Topic guides not submitted making it difficult to make an ethical judgement.
- Insufficient information about data handling and storage.
- PIS does not include detail about the use or handling of personal data.

5.1. Provision themes: Academic Lead Sponsor

- No emergency contact details provided in the PIS.
- The research summary A6-1 is not an accurate reflection of the research.

5.2. Provision themes: NHS or HSC Care Organisation Lead Sponsor

- Lone worker agreements not in place or produced.
- Insufficient information about whether the students/research team are allowed to access medical notes.
- Consideration hasn't been given to making study results available to participants.

Studies limited to working with data (specific project only)

6.0. Provision themes : All sponsor types

- Requirement for further information about who will access data and their permissions to do so.
- Insufficient information about the handling, storage, retention, use and destruction of data.
- Further detail required about the data transfer arrangements (inside and outside UK).
- Requirement to review the statistical analysis plan to ensure it will meet the study objectives.

Provision themes: Academic, Pharmaceutical, NHS or HSC Care Organisation Lead Sponsor

N/A all provision themes applied to all sponsor types.

Studies Limited to working with human tissue samples

7.0. Provision themes : All sponsor types

- Requirement for further information about the consent processes.
- Insufficient information about the handling and anonymisation of the samples and associated data.
- Requirement for further information about the transfer of the human tissue.
- Requirement for further information about the process if there are findings of clinical significance.

7.1. Provision themes: Academic

- No detail provided about the complaints procedure in the participant information sheets.

Provision themes: Pharmaceutical and NHS or HSC Care Organisation Lead Sponsor

N/A all provision themes applied to all sponsor types.

Basic Science

8.0. Provision themes: All Sponsor Types

- Insufficient information about arrangements for data storage.
- Requirement for further information about the arrangements for data sharing and transfer.

8.1. Provision themes: Academic Lead Sponsor

- PIS does not clearly state what the research procedures involve.

8.2. Provision themes: Pharmaceutical Lead Sponsor

- Insufficient information about the distress policy.
- Further detail required around the process if the study procedures gave rise to findings of clinical significance.

8.3. Provision themes: NHS or HSC Care Organisation Lead Sponsor

- Requirement to reference a complaints contact in the participant information sheets.
- Research summary not an accurate reflection of the study.

Other Study

9.0. Provision themes: All Sponsor Types

- Not enough information provided about the accessing, handling and movement of participant data.
- Requirement to provide detail about the distress policy.
- Detail required about how it would be handled if abuse was disclosed or apparent.
- Insufficient detail about the complaints contacts and who to call if distress is caused by a study procedure.
- Study summary (A6-2) not considered to be an accurate reflection of the study.

Provision themes: Academic, Pharmaceutical, NHS or HSC Care Organisation Lead Sponsor

N/A all provision themes applied to all sponsor types.

Current Communication Routes and Opportunities to Feedback Learning Points

Lead Sponsor Type	Key Learning Points	Current communication channels and meetings with sponsor	Relationship Leads	Suggested Communication Route
Pharmaceutical Industry	<ul style="list-style-type: none"> -Basic validation criteria (REC and Assessment) -Can be drawn from points: 1.0, 2.0, 2.1, 3.0, 3.2, 4.0, 4.2, 5.0, 6.0, 7.0, 8.0, 8.2 and 9.0. 	<ul style="list-style-type: none"> -P1AG -Collaboration and Development Forum -Transparency bi-annual mtg 	<ul style="list-style-type: none"> -Joan Kirkbride/Catherine Blewett Mary Cubitt/Jonathan F-B Tom Smith 	<ul style="list-style-type: none"> -Build points into training available to researchers (online/face to face) -Liaise with relationship leads to see if they have any additional suggested communication routes outside of those managed by the RES. -consider building learning points into the sponsor tool kit.
Medical Device Industry	<ul style="list-style-type: none"> -Basic validation criteria (REC and Assessment) -Can be drawn from points: 1.0 and 1.2 	<ul style="list-style-type: none"> -Researcher Training Days -Sponsor reference group 	<ul style="list-style-type: none"> Joan Kirkbride/Sheila Oliver Jonathan F-B/Will Bowen 	<ul style="list-style-type: none"> -Build points into training available to researchers (online/face to face) -Consider additional routes for sharing common errors information sheet with the medical device industry. -consider building learning

				points into sponsor tool kit.
NHS or HSC care organisation	<ul style="list-style-type: none"> -Basic validation criteria (REC and Assessment) -Can be drawn from points: 1.0, 1.3, 2.0, 2.3, 3.0, 3.1, 4.0, 4.3, 5.0, 5.2, 6.0, 7.0, 8.0, 8.3 and 9.0 	<ul style="list-style-type: none"> -REC staff relationships with local R&D dept. -Researcher Training Days -Social Care Institution of Excellence -NHS R & D forum -change leads (HRA approval) - research support champion meetings and quarterly working group meetings. 	<p>REC staff with existing relationships with their local NHS organisations. Joan Kirkbride/Sheila Oliver</p> <p>Sheila Oliver</p> <p>Janet Messer Mary Cubitt</p>	<ul style="list-style-type: none"> -Consider routes for sharing a common errors information sheet with local NHS R&D depts. -Ensure the learning points are built into the researcher traing day material. -Consider how learning points can be added into the e-learning modules which can be accessed by external stakeholders. -Liaise with relationship leads to see if they have any additional suggested communication routes outside of those managed by the RES. -consider building learning points into sponsor toolkit.
Academic	<ul style="list-style-type: none"> -Basic validation criteria (REC and Assessment) -Can be drawn from: 1.0, 1.1, 	<ul style="list-style-type: none"> -REC staff relationship with University R&D dept. 	<p>REC staff with existing relationships with their local University R and D dept.</p>	<ul style="list-style-type: none"> -Consider routes for sharing a common errors information sheet with local NHS R&D depts.

	2.0, 2.1, 3.0, 3.1, 4.0, 4.1, 5.0, 5.1, 6.0, 7.0, 7.1, 8.0, 8.1 and 9.0.	<p>-Some DRM presentations/ workshops at local Universities.</p> <p>- Researcher Training Days</p> <p>-Sponsors Reference Group</p> <p>-Association of Research Ethics through C & D Forum</p> <p>NCSRg meetings, ad hoc feedback</p>	<p>DRMs who have previously presented/conducted workshops at local Universities.</p> <p>Joan Kirkbride/Sheila Oliver</p> <p>Jonathan F-B/Will Bowen</p> <p>Jonathan F-B/Will Bowen</p> <p>Jonathan F-B, Catherine Blewett, Charlotte Allan.</p>	<p>-Consider re-instating DRM visiting local Universities to present/hold workshops.</p> <p>-Ensure the learning points are built into the researcher training day material.</p> <p>-Consider how learning points can be added into the e-learning modules which can be accessed by external stakeholders.</p> <p>-Liaise with relationship leads to see if they have additional suggested communication routes outside of those managed by the RES.</p> <p>-Consider building learning points into sponsor tool kit.</p>
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Research Ethics Committee function Learning Points and Opportunities for Improvement

The letters reviewed showed a clear commitment from the Research Ethics Committee operation to provide an efficient and robust service. The thoroughness of the ethical review and guidance given to researchers demonstrated the protection and promotion of the interests of the patients and public in health and social care research.

A number of opportunities to improve the REC functions consistency and effectiveness were identified.

Observation	Example (s)	Opportunities for Improvement
Incorrect Decision (PO instead of FOWC)	2x provisions were: "1. With regard to the Consent Form the Committee noted that the statements go from 4 to 6 and required an amended copy. 2. With regard to the Participant Information Sheet under the heading "Who has reviewed the study? The Committee required that medical ethics is amended to research ethics."	<ul style="list-style-type: none"> • Increase awareness of related SOPs and decision use in staff and REC members. • Increase awareness of the thresholds through the guidance document being developed. • Increase REC staff confidence in providing advice and steer to RECs when they are deciding on an opinion.
Could have easily been converted to a FOWC	Provisions given: "The Participant Information Sheet should be amended to reflect the following: a. P2 it states, "we think this treatment would be just as good". This was considered overly reassuring and should be amended. Care should be taken with the use of language, as a non-inferiority does not mean the same or as good as. b. P3 talks about 'your Doctor', it is unclear whether this is GP or Consultant. c. patients are allowed to withdraw from the trial at any time, e.g. day 3, but it is not clear in the PIS what the next step would then be.	<ul style="list-style-type: none"> • RECs to provide the wording they would find acceptable so that it can be checked at office level rather than going back to the sub-committee. • RECs to point to wording in a different area of the submission so that it can be a condition not a provision. • e.g. please add the detail of the procedures given at q ** of the IRAS form to the participant information sheet under the header 'What will I need to do?' • RECs to point to existing guidance so that it can be a condition not provision. E.g. please

	<p>Clarification is sought on whether they would always be referred back to their treating physician to decide on next step treatment. Please submit the revised document for review. 2. The GP letter should be amended to include detailed contact information for the research team,”</p>	<p>reformat the information sheet in line with the HRA guidance (include link).</p>
Unclear how provisions should be actioned	<p>“Provide clearly labelled professional Participant Information Sheets.”</p> <p>“Re-write PIS in plain English.”</p> <p>“The Committee wish to point out that it appears that the outcomes of the study depend on detailed analysis following the collection of data however very limited detail given in relation to the analysis.”</p> <p>“The Committee sought confirmation that there would be no coercion.”</p>	<ul style="list-style-type: none"> • RECs and REC staff to ensure that it is clear to applicants how they should proceed. I.E. Provide some context to the provision; make it clear what the REC require and why; make it clear if documentation changes are required; point to guidance and web links which would provide support.
Tone of letters could be improved.	<p>“The PIS was very uninformative”</p> <p>“Provide clearly labelled professional Participant Information Sheets.”</p> <p>“Re-write PIS in plain English.”</p>	<ul style="list-style-type: none"> • REC staff to ensure that the tone of correspondence is appropriate and supportive. • REC staff to point to guidance and web links which would provide support
Inappropriate request	<p>“Please provdie updated GCP training certificates.” (Basic Science)</p>	<ul style="list-style-type: none"> • Reminder issued in OMEA. • RECs and staff to remain abreast of the appropriate/inappropriate requests through management routes, QC, minute review, SHED, training and Chairs days..

Disproportionate attention to low risk issues.	22 x administrative PIS/Consent form changes requested for one study.	<ul style="list-style-type: none"> • RECs to consider the level of risk for participants and review proportionally. • HRA to encourage researchers and sponsor responsibility for the quality of their documentation. E.g. The REC noted a high number of grammatical and spelling errors in the participant information sheet. Please review and amend the documentation.
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Next steps

Internal Driven Improvements

- Review the internal learning points and consider how best to take them forward with RECs and REC staff to improve consistency.
- Consider how the learning points can be embedded into member/staff training (online and face to face).
- Undertake a review of the HRA owned guidance (website and IRAS) to see if there are any areas where the commonly made mistakes could be better addressed pre-emptively.
- Consider if any of the commonly raised provisions could reasonably be picked up by staff (REC or assessment) and addressed by researchers prior to the REC review.

Externally Focused Improvements

- Consider how the HRA can support external learning and encourage the submission of better quality applications.
- Consider the possible routes for feeding back specific learning points to sponsor types and the research community. Are we reaching who we need to?
- Refer to the stakeholder map and liaise with the relationship lead to get their view on how best to feedback.
- Consider the suggested feedback route and strategy and the resources (material and staff) required.
- Consider if/how findings could be filtered into the sponsor tool kit being developed moving forward.
- Consider how to ensure the learning points filter into the online training accessible to researchers.