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Optimisation of pharmacy content in clinical cancer research protocols: experience of the United Kingdom Chemotherapy and Pharmacy Advisory Service (CPAS)

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P.R. Debruyne[1,2*], P.J. Johnson[3], L. Pottel[1,2], S. Daniels[4], R. Greer[5], E. Hodgkinson[6], S. Kelly[7], M. Lycke[1,2], J. Samol[8], J. Mason[9], D. Kimber[10], E. Loucaides[11], M.K.B. Parmar[12] and S. Harvey[13] on behalf of NIHR CRN – CPAS

[1]Ageing & Cancer Research Cluster, Centre for Positive Ageing, University of Greenwich, London, UK; P.Debruyne@greenwich.ac.uk; [2]Cancer Centre, General Hospital Groeninge, Kortrijk, Belgium; Philip.Debruyne@azgroeninge.be; Lies.Pottel@azgroeninge.be; Michelle.Lycke@azgroeninge.be; [3]Department of Molecular and Clinical Cancer Medicine, University of Liverpool, Liverpool, UK; Philip.Johnson@liverpool.ac.uk; [4]Pharmacy and Medicines Management, University College London Hospitals, London, UK; Susanna.Daniels@uclh.nhs.uk; [5]Leeds Teaching Hospital NHS Trust, Leeds, UK; Rachel.Greer@leedsth.nhs.uk; [6]Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, UK; Elizabeth.Hodgkinson@sth.nhs.uk; [7]Pfizer Oncology UK, Walton Oaks, Tadworth, UK; Stephen.J.Kelly@pfizer.com; [8]St George's Hospital Healthcare NHS Trust, London, UK; Jenssamol@gmail.com; [9]Sandwell and West Birmingham Hospitals NHS Trust, West Midlands, UK; Pharmacy and Therapeutics, University of Birmingham, Birmingham, UK; J.Mason@bham.ac.uk; [10]Wessex Clinical Senate & Strategic Networks, NHS England, Southampton, UK; D.Kimber@nhs.net; [11]Senior Executive, NCRI Clinical Studies Groups, London, UK; Eileen.Loucaides@cancer.org.uk; [12]MRC Clinical Trials Unit at UCL, University College London, London, UK; M.Parmar@ucl.ac.uk or M.Parmar@ctu.mrc.ac.uk; [13]NIHR CPAS, National Institute for Health Research, Clinical Research Network Cancer Coordinating Centre, Leeds, UK; Sally.Harvey@nihr.ac.uk

***Corresponding author:** Dr. Philip R. Debruyne, Department of Adult Nursing & Paramedic Science, Faculty of Education & Health, University of Greenwich, Avery Hill

Campus, Grey Building, Avery Hill Rd., Eltham, London, SE9 2UG, UK; Cancer Centre, General Hospital Groeninge, Loofstraat 43, B-8500 Kortrijk; T: +32(0)56633900; F: +32(0)56633909 E: P.Debruyne@greenwich.ac.uk, Philip.Debruyne@azgroeninge.be

ABSTRACT

Background: Clarity and accuracy of the pharmacy aspects of cancer clinical trial protocols is essential. Inconsistencies and ambiguities in such protocols have the potential to delay research and jeopardize both patient safety and collection of credible data. The Chemotherapy and Pharmacy Advisory Service (CPAS) was established by the UK National Cancer Research Network (NCRN), currently known as National Institute for Health Research Clinical Research Network (NIHR CRN), to improve the quality of pharmacy-related content in cancer clinical research protocols. This paper reports the scope of CPAS, its methodology of mandated protocol review and pharmacy-related guidance initiatives, and its current impact.

Methods: Over a 6-year period (2008-2013) since the inception of CPAS, cancer clinical trial protocols were reviewed by the service, prior to implementation at clinical trial sites. A customised Review Checklist was developed and used by a panel of experts to standardise the review process, and report back queries and inconsistencies to chief investigators. Based on common queries, a Standard Protocol Template comprising specific guidance on drug-related content and a Pharmacy Manual Template were developed. In addition, a guidance framework was established to address 'ad hoc' pharmacy-related queries.

The most common remarks made at protocol review have been summarized and categorized through retrospective analysis. In order to evaluate the impact of the service, chief investigators were asked to respond to queries made at protocol review and make appropriate changes to their protocols. Responses from chief investigators have been collated and acceptance rates determined.

Results: A total of 176 protocols were reviewed. The median number of remarks per protocol was 26 of which 20 were deemed clinically relevant, and mainly concerned the drug regimen, support medication, frequency and type of monitoring, and drug supply aspects. Further analysis revealed that 62% of chief investigators responded to the review. All responses were positive with an overall acceptance rate of 89% of the proposed protocol changes.

Conclusion: Review of pharmacy content of cancer clinical trial protocols is feasible and exposes many undetected clinically relevant issues that could hinder efficient trial conduct. Our service audit

revealed that the majority of suggestions were effectively incorporated in the final protocols. The refinement of existing, and development of new pharmacy-related guidance documents by CPAS might aid in better and safer clinical research.

KEY WORDS: chemotherapy, pharmacy aspects, cancer, clinical trials, quality control

INTRODUCTION

Approximately 14 million adults worldwide were diagnosed with cancer in 2012, 8.2 million of them died because of the disease. In the United Kingdom (UK) 396 per 100 000 people were confronted with a cancer diagnosis in that same year. It is estimated that the incidence of cancer will increase another 55% and 35% for men and women, respectively, between 2007 and 2030 due to growth and ageing of the population.[1, 2] At present, the cancer research UK website, which aims to list all cancer trials and studies recruiting in the UK, registered 1884 trials, a number that is more likely to increase rather than decrease in the near future.[3]

The success of a clinical trial largely depends on the quality of its protocol.[4] Incompleteness, inconsistencies or errors in a protocol may impact the proper conduct of a trial with subsequent risk to patient safety and ultimately accuracy of results. As a response to the inadequacy of current research protocols, Chan et al. recently published guidance in the form of a checklist of recommended items to include in a clinical intervention trial protocol, though it did not include pharmacy-related content.[5] The latter is, however, an essential part of any clinical trial involving investigational medicinal products. Moreover, it is especially important in cancer trials, where the drugs used may be cytotoxic and/or form part of a complex treatment regimen involving multiple drugs, administered in particular orders over a number of days and frequencies.

Some pharmacists had the impression that poor study design and poor pharmacy content in protocols was creating a substantial workload and hindering the set up and running of clinical trials. Delays were being caused by issues including choice of inappropriate infusion solutions, inappropriate volumes for infusion of cytotoxic doses, enforced use of inappropriate packaging and labelling of drug supplies, and complicated funding and purchasing arrangements agreed between the pharmaceutical companies and the trial organizing bodies.[6] In the past, oncology pharmacists also frequently reported organizational

issues and inconsistencies in clinical trials, often related to various protocol interpretations due to differences in hospital local practices. Some of these inconsistencies may have put patients at unnecessary risk of errors, increased the workload for pharmacy and nursing staff, as well as jeopardized accuracy of the trial outcome.

The rising number of cancer clinical trials, the more stringent national and international legislation and Good Manufacturing Practice requirements, combined with the increasing demand for pharmacy support prompted the National Cancer Research Network (NCRN; currently known as National Institute for Health Research Clinical Research Network (NIHR CRN)) to form a standardisation committee in 2003, which evolved into the current Chemotherapy and Pharmacy Advisory Service (CPAS) by the end of 2007.[7, 8]

It was set up to advise chief investigators, clinical trials units and clinical studies groups on the chemotherapy- and pharmacy-related content of their protocols, in order to maintain and enhance research quality and thereby aid development of high-quality research protocols. The aim was firstly to involve pharmacists, clinicians, nurses and pharmacy technicians at the early stages of protocol design to address problems with the protocol and underpin the ability of hospital pharmacies to support clinical trials of new and established drugs. Secondly, it was intended that through a transparent cycle of continuous improvement and feedback, the learning from the service would eventually mean that it was no longer required.

Currently, CPAS constitutes a multidisciplinary national team of pharmacists, research nurses, haematologist and oncologists. It has a formal remit to: (1) consider trials to be adopted by the NIHR CRN and review draft protocols, (2) provide support to investigators and others about medicine-related issues in oncology/haematology trials, (3) review published evidence to help standardise chemotherapy administration in clinical trials (e.g. addressing generic issues such as dosage modifications in organ dysfunction, calculations of body surface area, modifications for obesity, etc.). CPAS reviews are mandatory for all new drug

trials approved by the Cancer Research UK Clinical Trials Awards and Advisory Committee and the National Institute for Health Research Health Technology Assessment programme. The mandatory process does not involve Medical Research Council funded trials and industry-funded studies but they can be submitted for review on a voluntary basis.

This paper describes the establishment of the service, its methodology, the retrospective review of its activities for the first six years (from January 2008 until December 2013) and analysis of the responses from chief investigators to issues raised at review.

METHODS

CPAS: the organisation

The CPAS core comprises four *ex officio* members, or non-reviewers, namely the chair, the representatives of respectively the NIHR CRN and National Cancer Research Institute (NCRI) clinical studies group secretariat, and an NIHR CRN pharmacy advisor. The latter serves as the main point of contact and liaison between researchers and CPAS, and coordinates CPAS activities and the advisory service as a whole. At present, CPAS membership includes 50 Panel and 15 Committee members, consisting of 37 pharmacists, 13 clinicians, 5 research nurses, 5 pharmacy technicians, 1 clinical trials unit manager, and the four core Committee members. All CPAS non-core members are responsible for protocol reviewing and other protocol- or pharmacy-related queries. The Committee members also fulfil a strategic decision-making role.

Review of draft protocols

A Review Checklist was developed based on a literature review on clinical drug research guidelines, medication errors in cancer chemotherapy, and common pharmacy-related issues. The checklist was developed to standardise the conduct of reviews by the CPAS panel of

experts, and was used to report back queries and inconsistencies to chief investigators. The current checklist consists of 12 sections with a total of 119 questions (**Supplementary Online Appendix 1)**.[9] The sections include: (1) regimen (nomenclature, etc.), (2) support medication, (3) dose calculation, (4) inclusion/exclusion criteria, (5) randomisation, (6) monitoring, (7) dose modification/delay, (8) drug information/concomitant medication, (9) drug administration, (10) drug supplies, (11) drug accountability/drug returns and (12) general. The first 11 categories are considered to be of clinical significance whilst the 12th category pools comments that are related to the general formatting and grammar, trial administration or financial issues. Reviewers are encouraged to add any relevant comments not covered by the standard checklist.

A draft protocol can be submitted for review at any point after funding approval, once the drug treatment section of the protocol is near completion, but no later than two months prior to multi-centre research ethics committee submission (**Figure 1**). Initially, a minimum of three reviewers, of which at least one was an oncology pharmacist, reviewed each protocol in parallel. Currently, the number of reviewers for each protocol averages five, namely one clinician, a research nurse, and three pharmacists with different subspecialties. Reviewers are given two to three weeks turn-around time. The pharmacy advisor receives, collates and edits all final reviews into one anonymised document and returns it to the respective chief investigator within four to six weeks of submission. Whether or not the recommendations are incorporated into the final protocol remains at the chief investigator's discretion.

Support to investigators about medicine- and pharmacy-related content

In addition to its review activity, CPAS provides pharmacy-related support, either by direct contact or through guidance documents to assist protocol writing. First, a Standard Protocol Template, detailing specific 'Guidance on the drug-related content of clinical trial protocols'

was created based on the aforementioned Review Checklist and finalised in 2008.[10] It is subdivided into 8 sections: (1) trial procedures, (2) treatment of patients, (3) trial drugs, (4) glossary of formulae, (5) suggested capecitabine dose banding table, (6) manipulation of investigational medicinal products in the pharmacy, (7) labelling of investigational medicinal products and (8) note on oral anti-cancer therapy. It provides useful examples of phrases that could be incorporated in a protocol. A copy of the document can be found as the **Supplementary Online Appendix 2**, or on the website of the NIHR CRN.[10]

Second, in June 2009, a Pharmacy Manual Template was created for guidance to investigators with the content of pharmacy manuals for clinical trials.[11] It contains the following sections: (1) contact details of sponsor, (2) trial synopsis, (3) study medication, (4) randomisation, (5) prescribing, (6) dispensing, (7) accountability forms, (8) patient returns, (9) destruction, (10) hazards and (11) forms/templates. All documents are available online for use by others via the NIHR CRN website, or in the **Supplementary Online Appendix 3**. Last, as a unique group of national 'experts', CPAS, are available to answer 'ad hoc' questions addressing pharmacy-related queries, or requests for advice, in relation to National Institute for Health Research portfolio studies. The queries range from specific study-related questions to general trial-related questions (e.g. use of electronic prescribing system, patient randomisation faxes, transportation of refrigerated IMPs between hospital and satellite unit), and can be submitted to the pharmacy advisor. The pharmacy advisor considers the incoming queries and contacts relevant members of the CPAS panel for comment and advice. The comments are then collated into a final anonymised response based on consensus opinion. Where opinion varies, the different viewpoints and suggestions are discussed and a best practice approach is agreed. All queries and responses are stored for reference. This initiative has highlighted frequently posed questions which, for example, in March 2012 led to publication of an online investigational medicinal product statement[12] defining which drugs in a clinical trial protocol,

are classified as investigational medicinal products and which are non investigational medicinal products.

Retrospective analysis of protocol reviews

All protocol review reports returned to the chief investigators for the 6-year period between the 1st of January 2008 and the 31th of December 2013, were analysed retrospectively. A detailed list of all of the 176 protocols reviewed can be found on the CPAS page of the NIHR CRN website and in the **Supplementary Online Appendix 4**.[13] Trial characteristics were collected, and remarks that were retained in the final review report were summarized and categorized according to the twelve subsections of the Review Checklist described earlier.

Evaluation survey

At the time of receiving the final collated review for their protocol, a request was made to all chief investigators (i.e. those submitting their draft protocol for review) to provide feedback. They were asked to state whether or not they agreed with the issues raised at review and provide confirmation of changes made to their protocol as a result. A service evaluation audit was conducted to check chief investigator response rates and acceptance rates (% of remarks raised at review that were accepted and reflected in changes to the protocol) of proposed changes. This was done for all protocols reviewed in this 6-year period.

Statistical Analysis

Descriptive statistics were performed to present trial characteristics, frequency and type of remarks and response and acceptance rates. A response rate of 60% is considered as an acceptable level of response rate to surveys.[14] All analyses were conducted using Microsoft®

Excel 2011 (Microsoft Inc., Redmond, WA) and IBM SPSS v.19 (SPSS Inc.®, Chicago, IL) software.

RESULTS

Protocols reviewed by CPAS and findings

Trial characteristics of the 176 protocols that were reviewed, are described in **Table 1**. The median number of protocols per year reviewed was 27 (range 25 - 42) and appears to be stable over the years. Of these 4% were phase I trials, 51% were phase II trials, 25% were phase III trials, 1% were phase IV trials and 18% were combined phase I/II or II/III trials. The average time between submission of the protocol to CPAS and the return of the collated review was 35 days. This figure fluctuates between 21 days (and in one or two exceptional cases an excess of 80 days), depending on how busy CPAS service becomes at any one time.

The disease categories subdivided according to the respective clinical specialty groups are listed in **Table 1**. The included experimental treatment modalities concerned mainly cytotoxic chemotherapy (24%), molecular targeted therapy (24%) or a combination of drugs (36%). About 9% concerned studies of drug combinations with radiotherapy, 2% anti-hormonal treatment and 1% immunotherapy.

The review findings according to the 12 categories in the Protocol Review Checklist and the relative frequencies that each issue has arisen in the respective protocols are summarised in **Figure 2a and 2b**. The median number of remarks per protocol was 26 of which 20 were deemed clinically relevant. In our experience, the nature of the comments raised by reviewers fell into two broad categories: missing information and insufficient clarity of the information or guidance provided. The majority of clinically relevant remarks concerned the regimen (median [Q1,Q3]; 3 [1,6]), support medication (2 [1,4]), monitoring (2 [1,3]) and drug supply

aspects (2 [1,4]), and were the same over the years (**Figure 2a**). Some typical examples are listed in **Table 2.**

Service evaluation survey

A service evaluation survey was systematically sent to the respective chief investigators of which 62% responded. All responses were positive (qualitative responses; data not shown) which was reflected in a median overall acceptance rate of 89% of the by CPAS proposed protocol changes. Response rates and acceptance rates seemed to remain stable over the respective years (data not shown).

DISCUSSION

Cancer prevalence is high and will only increase in the near future. The quality of research protocols, in particular the pharmacy-related content, is of utmost importance to ensure cost-efficient, timely and safe research. To the best of our knowledge, an initiative like CPAS is unique, and such activities that aim to support chief investigators improve the pharmacy-related quality of cancer clinical trial protocols have not been published earlier. This paper describes the development of CPAS and reviews its activities from 2008 until 2013. The aim of CPAS is to raise awareness of the type, frequency and consequences of research protocol inadequacies, and to provide support to investigators either directly or in the form of guidance documents to assist the development of high quality clinical trial protocols.

CPAS was established in response to a general perception by our research community that pharmacy departments were a barrier to starting and running clinical trials especially those involving complex chemotherapy regimens. It was not the intention of pharmacy departments to hinder research and within our pharmacy community it was recognised that the workload generated by inadequate pharmacy information within protocols often caused resource issues

and subsequent delays to research.[15] A number of issues were raised that hindered trial implementation at the local level and which caused delays and problems in areas such as dose adjustments, dose capping, missing pharmacy information, supply of drugs and safe administration of chemotherapy.[6] Local practice often differs between hospitals causing inconsistent or wrong interpretation, which can negatively affect trial conduct and consequently data accuracy. Moreover, any missing or unclear protocol information has the potential to adversely affect patient safety. The remit of CPAS is, therefore, to resolve these issues at the draft protocol stage and achieve consistency across the clinical trial portfolio hosted by the NIHR CRN.

Qualitative evaluation of the CPAS review process, through the service evaluation survey, presented positive feedback. Indeed, the majority of investigators provided a written response to the final collated review, reporting that it was a helpful and constructive process that, in their opinion, reduced the number of protocol amendments that were required during the trial. The effectiveness of the service was also demonstrated by the remarkably high acceptance rate of the remarks raised by CPAS. The chief investigators accepted almost 9 out of 10 proposed amendments, which underscores the relevance of CPAS. While CPAS activities have been appreciated by the chief investigators of cancer clinical drug trials, the cost-benefit of this time-extensive review process is not verifiable at present. Future research could, therefore, prospectively examine whether an upfront pharmacy review process reduces the number of required pharmacy-related amendments, treatment-related protocol violations, or the percentage of treatment-related hospitalisations or deaths. Moreover, future work to inspect the characteristics of clinical drug trials where the chief investigators did not respond to review comments or incorporate suggested changes could identify areas of further guidance or educational resource that CPAS could provide. Retrospective analysis did, at present, not reveal any differences in trial phase, clinical specialty group or type of investigational therapy

between cooperative and non-cooperative chief investigators (data not shown). The latter might have been reluctant to wait for CPAS feedback, since it is recognised that the turn-around time for CPAS review and final collation could be seen as an addition of a substantial amount of time to an already lengthy protocol development period. As such, CPAS suggests that draft protocols are submitted as soon as possible and the review is conducted in parallel with other protocol development processes. Currently, the number of reviewers determined to scrutinise a draft protocol for CPAS is chosen to give a range of experience, specialities and views from different regions in the UK. It is possible that future refinements to the Review Checklist and elaboration on the detail of guidance documents already provided, might reduce the number of reviewers required and/or the time period of the review process.

Our systematic retrospective analysis indicated that a median of 26 remarks were suggested per protocol, and that the majority of remarks addressed by the reviewers were deemed clinically relevant. To our knowledge, this is the first time that such information, based on the use of a customised Review Checklist, is available. A formal request for more information about the protocol review process was sent to several cancer cooperative networks, however, only reciprocated by the National Cancer Institute and the Swiss Group for Clinical Cancer Research. Industry-funded trials or trials executed within a large cooperative group often provide in-house protocol review by scientific disease-specific committees, not always incorporating a pharmacist. However, there is only limited or no transparency regarding the protocol review process, and it thus serves to no benefit to external (academic) investigators. Our results indicate that the most frequently observed inconsistencies concerned the drug regimen, support medication, monitoring and drug supply aspects, thus highlighting the importance of collaboration between the oncology physician and clinical pharmacist at time of protocol design. CPAS protocol review included trial protocols of all phases, an extensive number of clinical specialty groups and a wide variety of cancer treatments. Results might,

however, not be extrapolable to commercially-funded trials. Future prospective research, addressing trials sponsored by industry and different funding agencies, might be useful to explore the potential for differences in protocol quality.

Over the years that CPAS has been operating, the number of review remarks per protocol appears to have remained stable. This fact could indicate that CPAS is unlikely to become redundant in the future. On the other hand, it could also suggest that CPAS guidance documents and checklists are not well-known by investigators and the CPAS advisory function not well utilised. There are many factors involved in determining why an organisation does not learn from previous experience and these could be explored by CPAS to maximise their effectiveness. Sensitisation of other cooperative groups in oncology and other medical subspecialties might also be required to ensure a more wide-spread implementation of CPAS knowledge in the future. Continuous service evaluation audits and evaluation of the activities will no doubt lead to further service improvements and adaption of CPAS tools. Moreover, with growth the number of activities performed by CPAS may also further expand to include advice on practical clinical trial issues relevant to pharmacists, such as dose-banding, chemotherapy stability and compatibility issues, and the incidence and avoidance of chemotherapy medication errors.

In conclusion, we have described the development and activities of CPAS. Systematic analysis of mandated reviews of pharmacy-related aspects of cancer clinical trial protocols proved to be useful and improved the quality of the clinical trials hosted by the NIHR CRN. Moreover, with the refinement of previously published CPAS guidance, development of new CPAS guidance and lessons learned from the review process itself, we hope that this paper will lead to a more wide-spread implementation of our knowledge by other academic groups and better, safer clinical research.

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Legends, tables, figures and Supplementary Online Appendices and Table

Figure 1. Diagram showing the typical protocol development timelines.

CTAAC: Clinical Trials Awards and Advisory Committee, FSC: Feasibility Study Committee, HTA: Health Technology Assessment Programme, MREC: Multi-centre Research Ethics Committee

Figure 2a. Number of remarks per review category per protocol, presented as boxplots, graphically displaying median, inter-quartile range and minimum and maximum data values; **Figure 2b.** Relative frequency of remarks per review category presented as a pie chart.

Table 1. Characteristics of the clinical trials reviewed between 2008 and 2013

Table 2. Examples of common relevant findings

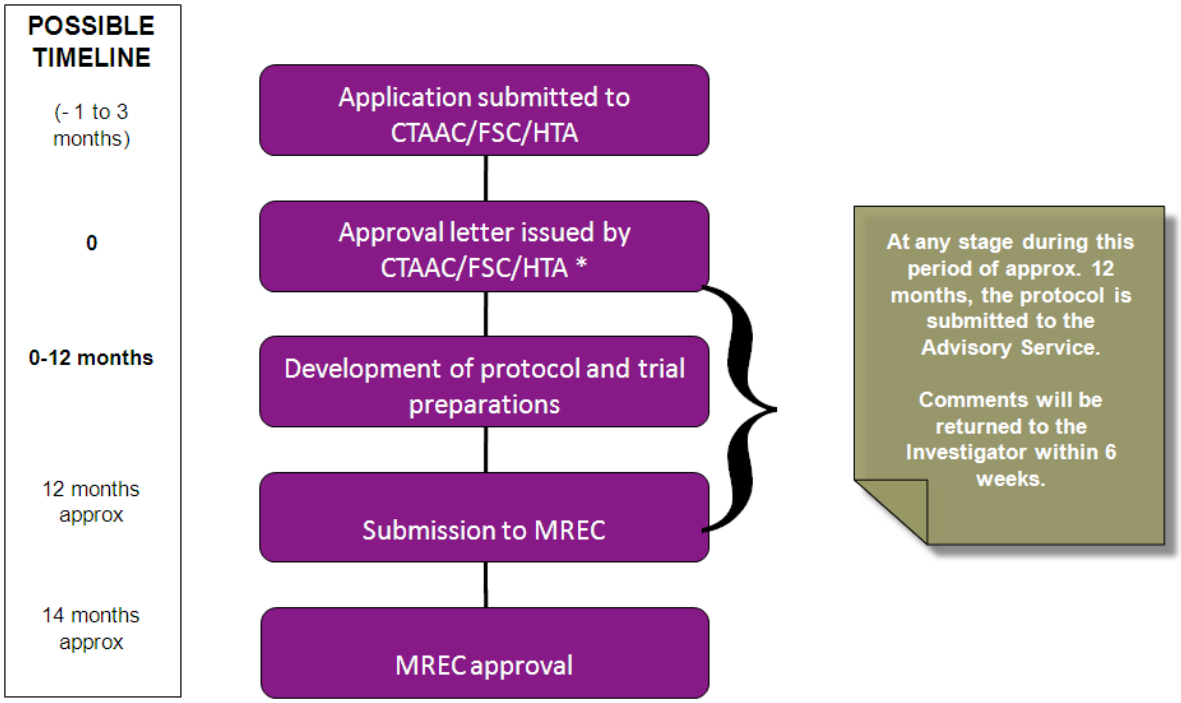
Supplementary Online Appendix 1. CPAS Protocol Review Checklist – Protocol review guidelines

Supplementary Online Appendix 2. CPAS Standard Protocol Template, version 2 updated March 2012

Supplementary Online Appendix 3. CPAS Pharmacy Manual Template, version 3 updated March 2012

Supplementary Online Appendix 4. A detailed list of the 176 protocols reviewed by CPAS

426 **Figure 1. A Diagram Showing the Typical Protocol Development Timeline**



427 * (containing guidance on submitting the protocol to the Chemotherapy and Pharmacy Advisory Service)

Figure 2a. Number of remarks per review category per protocol

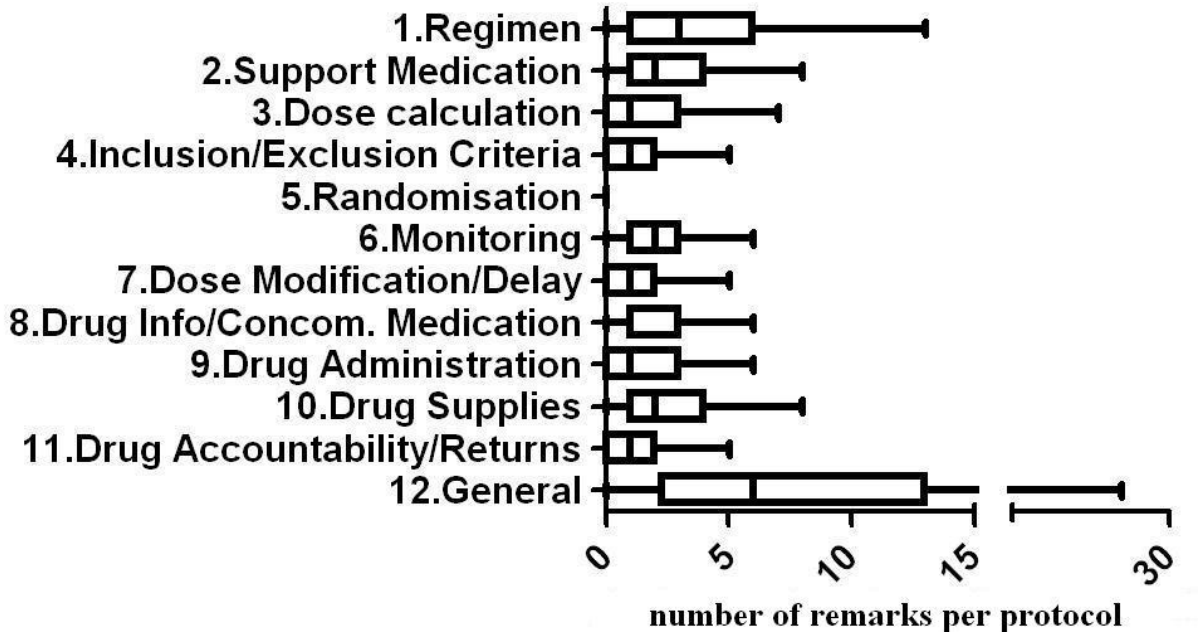
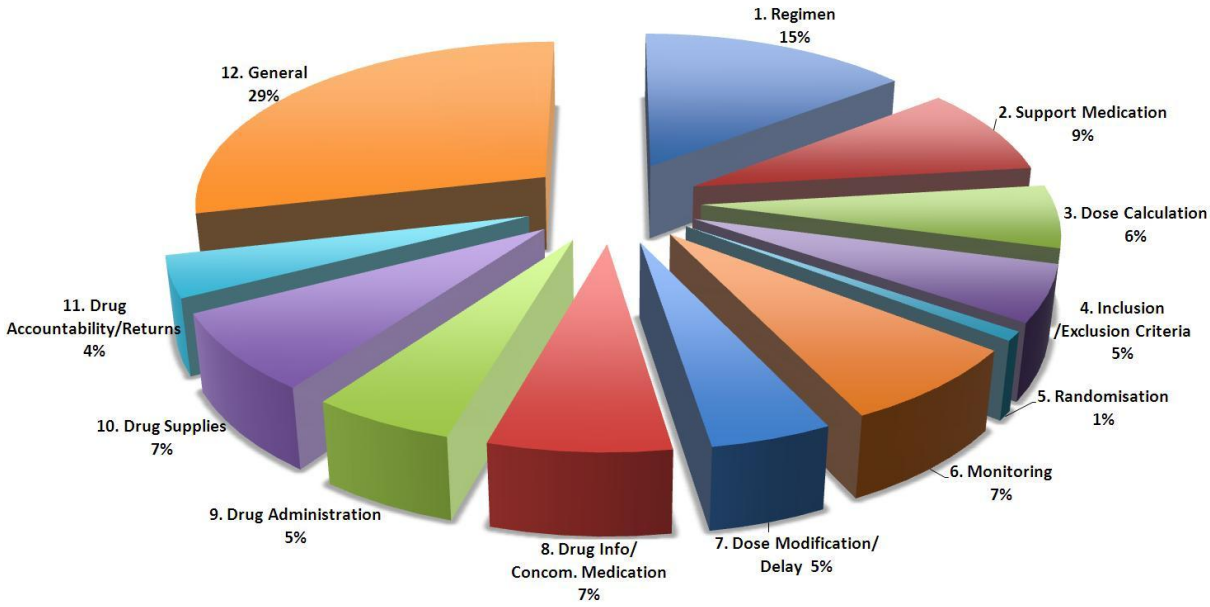


Figure 2b. Relative frequency of remarks per review category presented as a pie chart.



437 **Table 1. Characteristics of the clinical trials reviewed between 2008 and 2013**

	Studies (N= 176)	
Characteristic	No.	%
Year of Review		
2008	29	16
2009	26	15
2010	28	16
2011	42	24
2012	25	14
2013	26	15
Type of trial		
Phase I	7	4
Phase I/II	19	11
Phase II	90	51
Phase II/III	13	7
Phase III	44	25
Phase IV	1	1
Other	2	1
Clinical Specialty Group		
Biomarkers & Imaging	0	0
Bladder (including penile)	9	5
Brain	11	6
Breast	16	9
Children's Cancer and Leukaemia	3	2
Colorectal	14	9
Gynaecological	16	9
Haematological Oncology	26	15
Head and Neck	6	3
Lung	10	6
Lymphoma	13	7
Melanoma	7	4
Palliative and Supportive Care	1	1
Primary Care	0	0
Prostate	8	5
Psychosocial Oncology	0	0
Renal (including adrenal)	7	4
Sarcoma	8	5
Teenage and Young Adults	0	0
Testis	2	1
Upper Gastro-Intestinal (including pancreas and liver)	10	6
Combined	9	5

Type of investigational Therapy		
Cytotoxic chemotherapy	43	24
Hormonal therapy	3	2
Molecular targeted therapy	42	24
Immunotherapy	1	1
Combination of drugs	63	36
Combination with Radiotherapy	15	9
Other	9	5

438 **Table 2. Examples of common relevant findings**

Regimen
• No information on which drugs are IMPs and therefore which need accountability • Information missing on infusion times, stability of a product, diluents, use of non-PVC infusion bags and giving sets • Information missing on what to do if a patient vomits following a dose or misses a dose • Use of brand names instead of generic • Use of drug names that are not used in the UK e.g. acetaminophen instead of paracetamol • Information copied from previous protocol resulting in incorrect information being stated
Support medication
• No advice given for supportive medicines e.g. pre-meds, anti-emetics, hydration etc • 2mg/L Magnesium sulphate and 20mmol post-hydration bags insisted on by protocol (2mg/L = 0.008mmol Magnesium per litre)
Dose calculation
• No information on frequency of re-calculation of BSA or formula to use, re-calculation of GFR and method of GFR calculation • No reference to dose banding • Dose banding table of chemotherapy with doses expected to be measured to 2 decimal places
Monitoring
• Information missing on haematological and biochemical monitoring • Different cut-offs specified in different areas of the protocol for discontinuing a drug due to renal impairment • Screening investigations specified to be carried out within 14 days of treatment. Schedule of events table did not make this clear

Drug administration
• Incorrect description of drug administration • Different drug preparation available, incorrect choice made for route of administration required • Proposed drug administration is not feasible in the specific study population

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