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

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35

36 **ABSTRACT**

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

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

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

56 **Results:** A total of 176 protocols were reviewed. The median number of remarks per protocol was 26  
57 of which 20 were deemed clinically relevant, and mainly concerned the drug regimen, support  
58 medication, frequency and type of monitoring, and drug supply aspects. Further analysis revealed that  
59 62% of chief investigators responded to the review. All responses were positive with an overall  
60 acceptance rate of 89% of the proposed protocol changes.

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

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

66

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

68

## 69 INTRODUCTION

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

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

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

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

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

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

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

119 trials approved by the Cancer Research UK Clinical Trials Awards and Advisory Committee  
120 and the National Institute for Health Research Health Technology Assessment programme.  
121 The mandatory process does not involve Medical Research Council funded trials and  
122 industry-funded studies but they can be submitted for review on a voluntary basis.  
123 This paper describes the establishment of the service, its methodology, the retrospective  
124 review of its activities for the first six years (from January 2008 until December 2013) and  
125 analysis of the responses from chief investigators to issues raised at review.

126

## 127 **METHODS**

### 128 **CPAS: the organisation**

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

139

### 140 **Review of draft protocols**

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

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

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

164

### 165 **Support to investigators about medicine- and pharmacy-related content**

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



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

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

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

196

### 197 **Retrospective analysis of protocol reviews**

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

204

### 205 **Evaluation survey**

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

213

### 214 **Statistical Analysis**

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

218 Excel 2011 (Microsoft Inc., Redmond, WA) and IBM SPSS v.19 (SPSS Inc.<sup>®</sup>, Chicago, IL)  
219 software.

220

## 221 **RESULTS**

### 222 **Protocols reviewed by CPAS and findings**

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

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

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

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

244

#### 245 **Service evaluation survey**

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

251

## 252 **DISCUSSION**

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

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

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

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

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

302 Our systematic retrospective analysis indicated that a median of 26 remarks were suggested  
303 per protocol, and that the majority of remarks addressed by the reviewers were deemed  
304 clinically relevant. To our knowledge, this is the first time that such information, based on the  
305 use of a customised Review Checklist, is available. A formal request for more information  
306 about the protocol review process was sent to several cancer cooperative networks, however,  
307 only reciprocated by the National Cancer Institute and the Swiss Group for Clinical Cancer  
308 Research. Industry-funded trials or trials executed within a large cooperative group often  
309 provide in-house protocol review by scientific disease-specific committees, not always  
310 incorporating a pharmacist. However, there is only limited or no transparency regarding the  
311 protocol review process, and it thus serves to no benefit to external (academic) investigators.

312 Our results indicate that the most frequently observed inconsistencies concerned the drug  
313 regimen, support medication, monitoring and drug supply aspects, thus highlighting the  
314 importance of collaboration between the oncology physician and clinical pharmacist at time  
315 of protocol design. CPAS protocol review included trial protocols of all phases, an extensive  
316 number of clinical specialty groups and a wide variety of cancer treatments. Results might,

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

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

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

341

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353



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408 **Legends, tables, figures and Supplementary Online Appendices and Table**

409

410 **Figure 1.** Diagram showing the typical protocol development timelines.

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

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

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

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

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

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

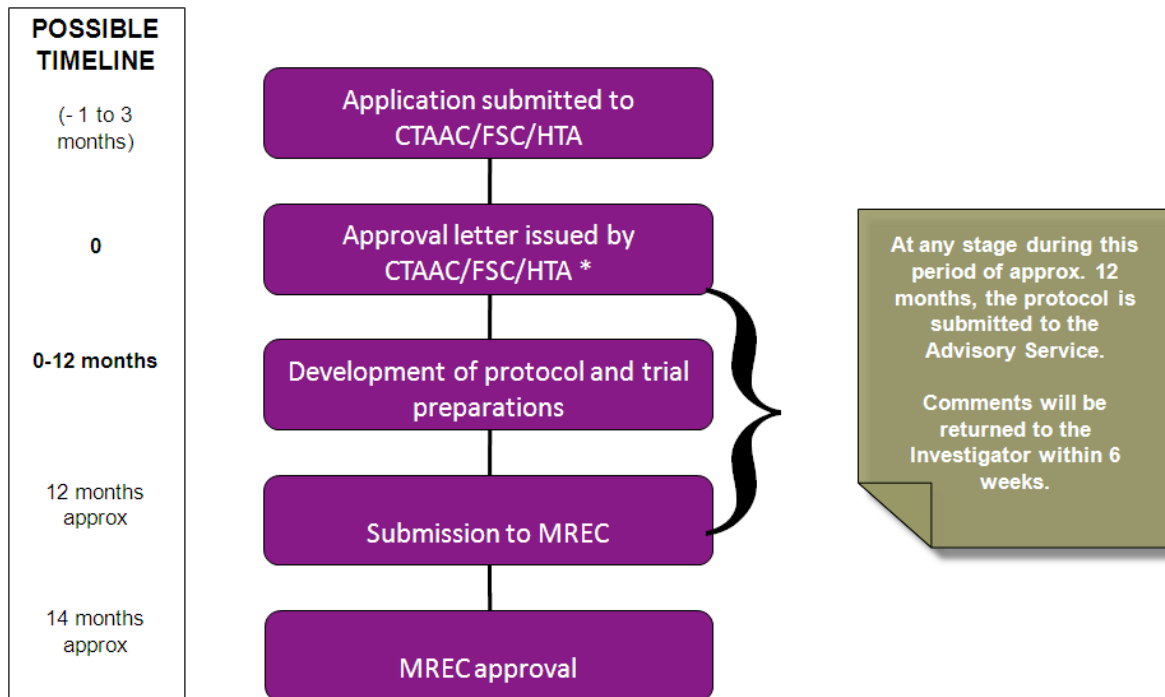
420 **Supplementary Online Appendix 2.** CPAS Standard Protocol Template, version 2 updated  
421 March 2012

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

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

425

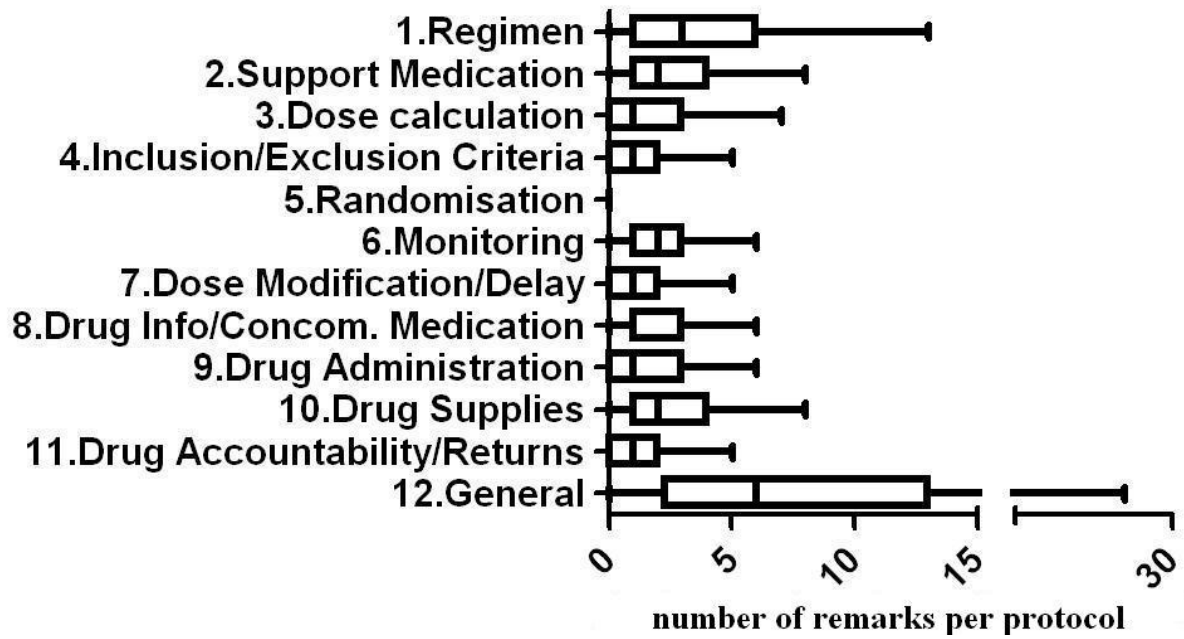
**Figure 1. A Diagram Showing the Typical Protocol Development Timeline**



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

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

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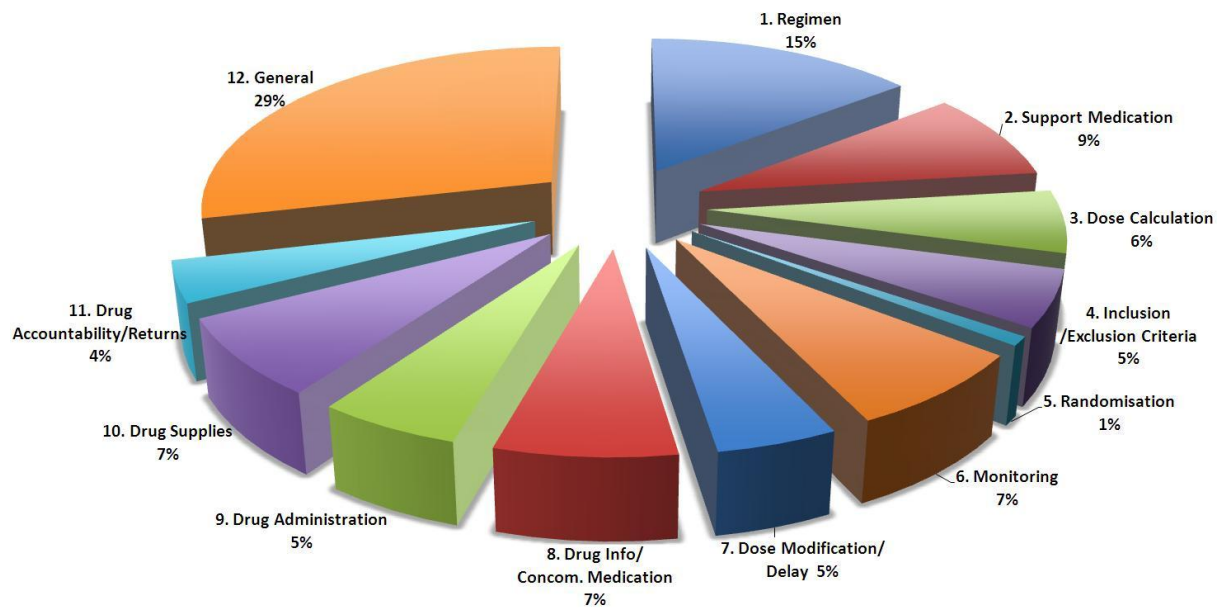
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**Figure 2b. Relative frequency of remarks per review category presented as a pie chart.**



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

<b>Characteristic</b>	<b>Studies (N= 176)</b>	
	<b>No.</b>	<b>%</b>
<b>Year of Review</b>		
2008	29	16
2009	26	15
2010	28	16
2011	42	24
2012	25	14
2013	26	15
<b>Type of trial</b>		
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
<b>Clinical Specialty Group</b>		
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

<b>Type of investigational Therapy</b>		
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

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

Regimen
<ul style="list-style-type: none"> <li>• No information on which drugs are IMPs and therefore which need accountability</li> <li>• Information missing on infusion times, stability of a product, diluents, use of non-PVC infusion bags and giving sets</li> <li>• Information missing on what to do if a patient vomits following a dose or misses a dose</li> <li>• Use of brand names instead of generic</li> <li>• Use of drug names that are not used in the UK e.g. acetaminophen instead of paracetamol</li> <li>• Information copied from previous protocol resulting in incorrect information being stated</li> </ul>
Support medication
<ul style="list-style-type: none"> <li>• No advice given for supportive medicines e.g. pre-meds, anti-emetics, hydration etc</li> <li>• 2mg/L Magnesium sulphate and 20mmol post-hydration bags insisted on by protocol (2mg/L = 0.008mmol Magnesium per litre)</li> </ul>
Dose calculation
<ul style="list-style-type: none"> <li>• No information on frequency of re-calculation of BSA or formula to use, re-calculation of GFR and method of GFR calculation</li> <li>• No reference to dose banding</li> <li>• Dose banding table of chemotherapy with doses expected to be measured to 2 decimal places</li> </ul>
Monitoring
<ul style="list-style-type: none"> <li>• Information missing on haematological and biochemical monitoring</li> <li>• Different cut-offs specified in different areas of the protocol for discontinuing a drug due to renal impairment</li> <li>• Screening investigations specified to be carried out within 14 days of treatment. Schedule of events table did not make this clear</li> </ul>

## 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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