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1 **Development of an Online resource for Recruitment Research in Clinical triAls**
2 **(ORRCA) to organise and map current literature**

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44 **Abstract**

45 **Background:** Recruiting the target number of participants within the pre-specified time frame
46 agreed with funders remains a common challenge in the completion of a successful clinical trial and
47 addressing this is an important methodological priority. While there is growing research around
48 recruitment, navigating this literature to support an evidence-based approach remains difficult.
49 ORRCA aims to create an online searchable database of recruitment research to improve access to
50 existing evidence and to identify gaps for future research.

51 **Methods:** MEDLINE (Ovid), Scopus, Cochrane Database of Systematic Reviews (CDSR) and Cochrane
52 Methodology Register, Science Citation Index Expanded (SCI-EXPANDED) and Social Sciences Citation
53 Index (SSCI) within the ISI Web of Science and ERIC were searched in January 2015. Search strategy
54 results were screened by title and abstract, and full text obtained for potentially eligible articles.
55 Studies reporting or evaluating strategies, interventions or methods used to recruit patients were
56 included along with case reports and studies exploring reasons for patient participation or non-
57 participation. Eligible articles were categorised as: systematic reviews, nested randomised controlled
58 trials, and other designs evaluating the effects of recruitment strategies (Level 1); studies that report
59 the use of recruitment strategies without an evaluation of impact (Level 2); or articles reporting
60 factors affecting recruitment without presenting a particular recruitment strategy (Level 3). Articles
61 were also assigned to one, or more, of 42 predefined recruitment domains grouped under six
62 categories.

63 **Results:** More than 60,000 records were retrieved by the search, resulting in 56,030 unique titles
64 and abstracts for screening, with a further 23 found through hand searches. 4,570 full text articles
65 were checked; 2,804 were eligible. Six percent of the included articles evaluated the effectiveness of

66 a recruitment strategy (Level 1), with most of these assessing aspects of participant information,
67 either its method of delivery (33%) or its content and format (28%).

68 **Discussion:** Recruitment to clinical trials remains a common challenge and an important area for
69 future research. ORRCA provides a searchable, online database of research relevant to recruitment.
70 The project has identified the need for researchers to evaluate their recruitment strategies to
71 improve the evidence base and broaden the narrow focus of existing research to help meet the
72 complex challenges faced by those recruiting to clinical trials.

73 **Keywords**

74 Recruitment, randomised controlled trial, clinical trial, accrual, barriers and facilitators, recruitment
75 interventions

76

78 **Background**

79 The challenges associated with completing a successful clinical trial are numerous and varied.

80 However, a common problem lies in the recruitment of participants. Successfully recruiting the pre-

81 specified number of participants within the planned timeframe is difficult and can negatively impact

82 all stakeholders.^{1, 2} Since the reports by McDonald¹ and Bower² in the mid-2000s, there has been

83 significant investment in infrastructure³ to support clinical trials in the United Kingdom. However,

84 the challenge of achieving adequate recruitment remains.^{4, 5}

85 The importance of overcoming recruitment difficulties was identified as the top priority for

86 methodological research, in a Delphi survey of Clinical Research Collaborative registered Clinical

87 Trials Units in the UK in 2011-12.⁶ A lower than expected recruitment rate can delay the

88 identification and availability of effective treatments by decreasing the power of the study,

89 increasing time and costs required for trial delivery and in some cases leading to early termination of

90 studies. In 2011, 19% of trials on the National Library of Medicine registry were terminated early

91 citing accrual problems and an estimated 48,027 people were enrolled in trials that were unlikely to

92 meaningfully answer the primary research question due to insufficient number of participants.⁷

93 Lower than expected recruitment may be due to several factors, and strategies are often put in place

94 during trials to help improve the recruitment rate. As a result, the approaches used are responsive

95 and their impact might not be assessed.⁸⁻¹⁰

96 As recruitment to time and target is a challenge for many trials, efficient management of the

97 recruitment literature would allow trialists and methodology researchers to access and use relevant

98 information to improve recruitment to studies, assess the methods that have been used to evaluate

99 recruitment strategies and identify uncertainties that warrant further research. Currently, navigating

100 the published literature for evidence on recruitment strategies is difficult and time consuming.

101 CONSORT guidelines do not require published reports of Randomised Controlled Trials to describe
102 recruitment methods. Recruitment information may be poorly reported including only the minimum
103 amount of information to comply with the guidelines. Consequently most trial reports do not
104 provide a useful resource for identifying recruitment interventions. Recruitment issues might be
105 more likely to be reported if the trial is stopped early, thereby identifying barriers rather than
106 facilitators to recruitment. Furthermore, even if a trial report contains information on the effects of
107 a specific recruitment strategy, identifying such information in the tens of thousands of reports of
108 trials published each year would be an overwhelming task.

109 The ORRCA project (Online resource for Recruitment Research in Clinical triAls) aims to create an
110 online resource of research to help trialists and others to identify interventions relevant to specific
111 recruitment challenges. We describe the development of the ORRCA online database and summarise
112 the included literature in this paper.

113 **Methods**

114 The development of the ORRCA database involved three key steps: identification of relevant
115 literature, mapping of this literature to pre-specified recruitment research domains and extraction of
116 relevant data from included studies. These steps are described below.

117 **Search strategies and identification of literature**

118 A librarian assisted with the development of database specific search strategies (Supplementary File
119 1) based on those used by Treweek *et al.*^{11, 12} The search strategies were agreed by the Study
120 Management Group, made up of the co-applicants on this research project. The following databases
121 were searched during January 2015, with no restriction on language or publication date:

- 122 • Cochrane Database of Systematic Reviews (CDSR) and Cochrane Methodology Register
123 (CMR) as components of the *Cochrane Library* www.cochranelibrary.com

- 124 • MEDLINE via Ovid
- 125 • SCOPUS (including EMBASE)
- 126 • Education Resources Information Center (ERIC), CSA
- 127 • Science Citation Index Expanded (SCI-EXPANDED) , ISI Web of Science
- 128 • Social Sciences Citation Index (SSCI), ISI Web of Science

129 Additional references were found through hand searching systematic reviews of nested randomised
130 evaluations of recruitment interventions (Supplementary File 1).

131 **Inclusion and Exclusion Criteria**

132 Studies were included if they reported or evaluated recruitment strategies, interventions or
133 methods and if the full text of their report was available in English.

134 As well as studies of recruitment to randomised trials, articles reporting recruitment to other health
135 research designs such as cohort studies, observational studies, surveys, focus groups and biobank
136 donations were included as a source of transferable knowledge and ideas. However, the search
137 strategy was not focused on these areas.

138 A full list of exclusion criteria is available within Supplementary File 1.

139 **Identification and training of volunteer reviewers**

140 Screening of the identified materials was done by a team of volunteer reviewers identified through
141 the University of Liverpool Clinical Trials Research Centre, the Hub for Trials Methodology Network
142 Recruitment Working Group and the Health Research Board Trials Methodology Research Network.
143 Reviewers had methodological research experience, were provided with written guidance and
144 expected to attend a training session, in-person or by teleconference.

145 **Development of a schema of recruitment research domains**

146 A taxonomy of recruitment research themes was developed to categorise literature and map
147 research efforts. The taxonomy drew on existing work by Caldwell et al. who broadly grouped 37
148 trials of recruitment strategies that they had identified for a systematic review into four categories:
149 novel trial design; incentives; provision of trial information and recruiter differences⁸. An additional
150 two categories, “trial conduct” and “pre-trial activities”, (Figure 1) were added along with a
151 breakdown of domains within each category. The taxonomy was presented to the Hub for Trials
152 Methodology Network Recruitment Working Group and the Study Management Group for
153 agreement before being piloted, and was reviewed throughout the project to ensure relevance to
154 the emerging literature.

155 **Screening and Data Extraction**

156 Articles were screened by title and abstract across the team of reviewers. Ten per cent of abstracts
157 were independently checked for eligibility and rescreened by a different reviewer if more than 10%
158 of errors were identified. The full text of all potentially eligible articles was then obtained and
159 assigned a primary reviewer. A secondary reviewer was assigned to fifty percent of the articles to
160 ensure consistency across inclusion criteria, research domains and level of evidence. Inter-rater
161 reliability scores were not calculated due to the number of abstracts and full text articles. Queries or
162 disagreements were resolved through discussion with a third reviewer. Eligible articles were
163 categorised into each relevant recruitment domain and according to one of the following categories
164 of evidence:

165 **Level 1:** Systematic reviews, nested randomised controlled trials and case-control studies
166 evaluating the effects of recruitment strategies. This includes recruitment to hypothetical
167 trials and quasi-randomised studies.

168 **Level 2:** Studies that report recruitment strategies without an evaluation of impact.
169 This includes informal evaluations such as level of recruitment before and after a strategy is
170 applied.

171 **Level 3:** Articles that report possible factors affecting recruitment but do not present a
172 particular recruitment strategy. This includes studies evaluating reasons for participation or
173 non-participation, and lessons learnt from trials.

174 Included articles were not assessed for the quality of the evidence or risk of bias, a task left to the
175 database users due to the scale of the review.

176 Details of eligible articles and their categorisation were uploaded onto a free, publically accessible
177 website (www.orrca.org.uk) throughout the literature review process. Additional pre-specified
178 information for each eligible article was extracted. This information was used to populate search
179 filters that would allow users of the ORRCA website to refine searches and identify research relevant
180 to different populations and health conditions. (Supplementary Table S1). A free text search box on
181 the website homepage allows users to search across all article titles, abstracts and extracted data.

182 Articles initially coded as “other” (G1) were reviewed for the possible creation of new recruitment
183 domains, re-coding into existing domains or inclusion in the G1 domain.

184 **Analysis**

185 Analysis of articles was conducted in SAS 9.3 and SAS 9.4. Website use statistics for September 2016-
186 May 2017 were obtained using Google analytics. Search criteria and number of searches were
187 obtained from the ORRCA database, which anonymously records all searches performed in order to
188 evaluate uptake of the resource.

189 **Results**

190 More than 60,000 articles were identified through electronic databases with a further 23 articles
191 identified through hand searches. Following removal of duplicates, 56,030 titles and abstracts were
192 screened and 4,570 full text articles were reviewed. 2,804 articles were included in the online
193 database (Figure 2).

194 Included articles covered all Health Research Categorisation System ¹³ topic areas (Supplementary
195 Table S2), with cancer studies (25%) and mental health studies (13%) being the most frequent.
196 Articles covered recruitment research across the world although the majority reported recruitment
197 within North America (53%) or Europe (25%) with only 2% reporting information from Africa and 1%
198 from South America. Over half of the articles described recruitment of participants aged between 18
199 and 60 (51%) and a third focused on participants older than 60 (35%). There were relatively few
200 studies addressing recruitment of children under 16 years (12%) or aged between 16-18 years (7%).
201 The number of articles per year generally increased over time (Figure 3) and the majority were
202 published in journals focussed on clinical trials, cancer, epidemiology and family practice
203 (Supplementary Table S3).

204 1,883 articles were categorised as evidence 'level 3' (67%), with only 160 (6%) categorised as 'level 1'
205 and 761 (27%) as 'level 2'.

206 Studies could be relevant to more than one recruitment domain and on average each paper
207 contributed 2.5 domains, with 7060 domains recorded across the 2804 included articles (Table 1).
208 The most commonly populated domains were Barriers and Facilitators identified in Trial Conduct
209 (37%) and Pre-trial Planning (17%), Identification of Participants (26%) and Cultural and Minority
210 Considerations (16%). (Supplementary Table S4)

211 Articles included in evidence level 1 were most frequently categorised in domain category D
212 (Recruitment and Information Needs) with 53 evaluating the method of information delivery (33%)
213 and 44 (28%) evaluating the content and format of participant information. (Figure 4). No articles
214 evaluated the effects of interventions or strategies related to sample size estimation, the
215 importance of outcomes, organisation/ institutional factors or recruiter equipoise. Articles in
216 evidence levels 2 and 3 were most often categorised in the 'trial conduct' domain category
217 describing barriers and facilitators to recruitment.

218

219 **Website Use**

220 The online database was launched on the 1st September 2016 and is accessible via the website
221 www.orrca.org.uk. In the first nine months since the launch 1,058 searches of the database have
222 been undertaken with 1,139 users visiting the website from 18 countries (Supplementary Figure S1
223 and Table S5).

224 The most popular method of searching the database and filtering the literature was through the
225 recruitment domains (35%) followed by use of the free text search box on the homepage (23%)
226 (Supplementary Table S6). The most popular search filters addressing trial design or context were
227 health area (5%), recruitment approach (3%), health intervention type (3%), age (3%), recruitment
228 setting (3%) and host design (3%). The most frequently searched domains were B7 (Recruitment
229 Rate Prediction), and C3 (Barriers and Facilitators) (Supplementary Table S7). However, it is
230 important to note that during this analysis period ORRCA was used to support a systematic review of
231 recruitment rate prediction models and a priority setting exercise for evaluating recruitment
232 interventions (The PRioRiTy study).^{14, 15}

233 **Discussion**

234 Recruitment research in clinical trials remains a priority. The large number of articles identified for
235 inclusion in the ORRCA database and the extensive effort needed to identify them, together with the
236 subsequent use of the website, reinforce the need for a resource to enable trialists to access the
237 findings of relevant recruitment research. Mapping the research included in the database highlights
238 a continued emphasis on evaluating information for participants in clinical trials and a paucity of
239 evidence in other areas, in particular, the impact of outcome choice, trial site factors and recruiter
240 equipoise on recruitment.

241 Most domains identified in the eligible studies were contained within the Trial Conduct category,
242 reflecting the large number of case reports (evidence levels 2 and 3) of recruitment methods and

243 interventions. Several of the frequent domains were broad, such as Barriers and Facilitators (B10
244 and C3) and Trial Acceptability to Patients (B1). The relatively large number of articles on methods
245 for engaging cultural and ethnic minorities (C9) can be explained by the large representation of
246 North American research and the National Institute of Health's legislation mandating the inclusion of
247 women and minorities in research studies.^{16, 17}

248 Despite the increasing quantity of recruitment research, the evidence base for effective recruitment
249 strategies remains weak. A number of topics have not been considered but we recognise that some
250 of these will be difficult to assess through nested randomised studies or Studies within a Trial
251 (SWATs) and will require evaluation through other research methods. Domains such as
252 Organisation/Institution (C6) and Sample Size Estimation (B6) feature more prominently in articles
253 categorised as evidence levels 2 and 3, suggesting that trialists are aware of their importance and
254 are discussing their impact on recruitment but without doing high-level evaluations to investigate
255 them. In contrast, Recruiter Equipoise (E6), Trial Site Eligibility (B5), Trial Site Assessment (E5) and
256 the Importance of Outcomes to both recruiters (B9) and patients (B8) were rarely identified in the
257 eligible literature. Whilst there has been significant emphasis on giving greater consideration to the
258 choice of outcomes in clinical trials, including the development and selection of appropriate core
259 outcome sets^{18, 19} it appears that the impact of the choice of outcomes on recruitment is not yet a
260 subject of published research, although future studies may be planned²⁰.

261 An online survey of directors of Clinical Trial Units²¹ highlights a wide range of approaches used to
262 improve recruitment and the lack of evaluation of most of these. Systematic reviews of nested
263 randomised evaluations of recruitment interventions^{8, 11, 22} have shown the challenges of identifying
264 relevant literature, the inability of individual studies to demonstrate evidence for benefit¹¹ and the
265 variability in interventions. These issues make it difficult for studies to perform meta-analyses.^{8, 11} It
266 is perhaps not surprising, therefore, that, despite their relatively frequent evaluation within nested

267 randomised trials and systematic reviews, optimising the consent process and trial participant
268 literature continues to feature in the top ten priorities for recruitment research.^{14, 15}
269 More research is needed to strengthen the evidence base.^{9, 23, 24} However, concerns over the
270 perceived complexity of embedding methodological research studies, uncertainty as to how
271 potential funders will view the work, the impact on the host trial and concerns about the capacity of
272 the trial team to support them²⁴ may all be limiting their uptake despite the guidance and support
273 offered from initiatives such as the Studies Within A Trial^{25, 26} and MRC START.²⁷⁻²⁹ The new initiative
274 from the National Institute for Health Research Health Technology Assessment program to provide
275 up to £10,000 for embedded studies linked to HTA bids³⁰ will help within the UK. Practical guidance
276 on how to embed methodological research into host studies has also recently been published.³¹
277 Recruitment methods and information can affect subsequent patient retention, an area where there
278 is also a paucity of evidence for effective practices.³² Given concerns over the additional work
279 needed to embed methodological studies in host trials, exploration of the relationship between
280 recruitment and retention interventions is warranted to identify opportunities to run studies that
281 evaluate both recruitment and retention interventions at the same time.

282 The ORRCA database will be updated annually to ensure it remains a useful resource for addressing
283 recruitment challenges in trials, can support new systematic reviews and identify areas for future
284 methodological research. Authors and funding bodies are also encouraged to submit recently
285 published or ongoing studies through the website to avoid unnecessary duplication of effort.

286 **Strength and Limitations**

287 Comprehensive searches of multiple databases and the engagement of multiple reviewers have
288 allowed a large scale literature review. Although inclusion required access to an English language
289 publication, only 2% of potentially eligible full text articles were excluded due to the prohibitive
290 costs of translation and it is uncertain how many of these would have eventually met the inclusion

291 criteria. Furthermore, our extensive search strategies together with the characteristics of the eligible
292 articles, demonstrate that the online database and mapping exercise are internationally relevant.

293 The scale of the ORRCA project contributed to limitations within the coding approach. Reviewers
294 needed methodology research experience, received training and written guidance and were advised
295 to take an inclusive approach to coding domains. However, domain coding was complex given the
296 number of papers reviewed, the poor reporting and the lack of formalisation of recruitment
297 strategies within case reports. Users of the database are therefore encouraged to act as additional
298 reviewers and to recommend changes or coding of additional domains through the 'contact us'
299 section of the website.

300 Individual articles were assigned all relevant recruitment domains without any weighting in order to
301 create a simple and effective search functionality, Consequently, it is not possible to ascertain the
302 primary recruitment topic addressed in each article. Articles categorised within evidence level 1
303 (with the exception of systematic reviews) were allocated fewer domains on average, so this
304 problem largely impacts on articles at evidence levels 2 and 3 and, in particular, on case reports.

305 Although our search strategies focused on recruitment to clinical trials, a wider approach was taken
306 during the review process. Articles describing recruitment to other health research designs such as
307 cohort studies, biobanks and questionnaires were included to incorporate insights that might be
308 transferable to randomised trials. However, the database does not contain a comprehensive review
309 of recruitment strategies for non-randomised studies, and is limited to articles identified through the
310 search strategy that we adopted.

311 **Future research**

312 Mapping of the eligible recruitment research identifies unexplored areas which warrant further
313 evaluation. However, even frequently evaluated topics, such as patient consent information, still

314 need further research due to the current lack of conclusive evidence, which points to the need to
315 improve both the focus and rigour of future evaluations.

316 **Conclusion**

317 The ORRCA project involved undertaking an extensive review of the recruitment literature. Mapping
318 and analysis of the 2,804 articles in the initial version of the online database (www.orrca.org.uk)
319 provides insight into existing research efforts and highlights topics for future collaborative research,
320 promoting the reduction of waste in both methodology research and clinical trials. By successfully
321 engaging methodology researchers from across the UK and Ireland, we have demonstrated that
322 large scale collaborative methodological projects are possible.

323

324 *Supplementary File 1: Search strategies, exclusion criteria and hand searches*

325 *Supplementary File 2: Additional tables and figures*

326

327

328 **Competing interests**

329 The authors declare that they have no competing interests

330

331 **Authors Contributions**

332 CG conceived the project and is grant holder. JB, PB, MC, NH, NM, ST and PW were co-investigators
333 and gave project oversight as part of the study management group. NH and CG drafted the protocol,
334 developed the schema of recruitment domains and adapted the search strategies with input from
335 the HTMR recruitment working group (see acknowledgements). The recruitment working group
336 input was co-ordinated by co-chairs NH and LR. NH ran the initial searches and oversaw the abstract
337 screening process. AK oversaw the full text review and is coordinating the forthcoming update with

338 articles published between 2015 and 2016. AK and NH identified and trained volunteers for the full
339 text review. AK, NH, CB, WC, SD, HG, PH, LM, CR, and AV made substantial contributions to the full
340 text review and categorisation of articles. AK, CG and NH reviewed the results and categorisation of
341 articles. ARH analysed search data and assisted AK with statistical analysis of included literature. AK
342 drafted the initial manuscript with NH and CG. All authors inputted into the manuscript. CG is
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371

372 A full list of current reviewers is available at www.orrca.org.uk. Researchers with
373 methodological research experience can register interest in joining the review team through
374 the Contact Us section of the website.

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455 **Tables and Figures:**

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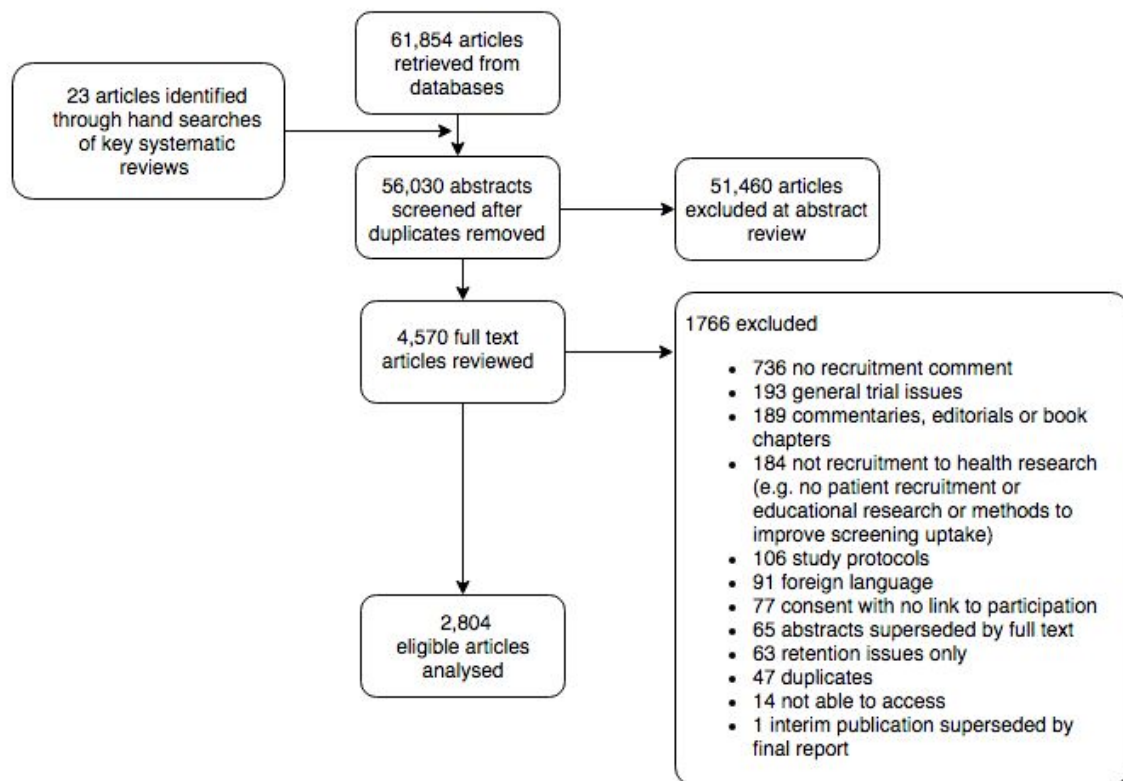
457 **Figure 1. Conceptual framework for recruitment research domains**

458 (See separate file)

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460 **Figure 2: ORRCA Literature Search**

ORRCA PRISMA Flow (For searches conducted in January 2015)



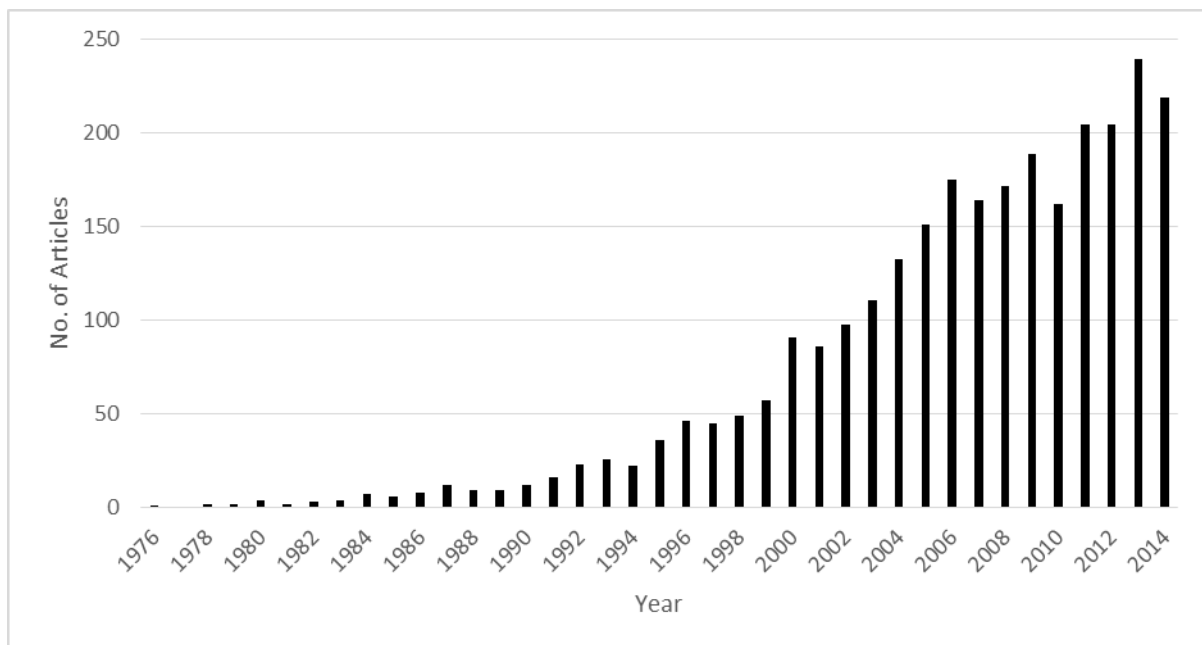
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465 **Figure 3: Year of Publication (n=2804)**



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470 **Table 1: Frequency of domains within domain categories and across evidence levels.**

Domain Category	Overall (2804 articles)		Evidence Level					
			Level 1 (160 articles)		Level 2 (761 articles)		Level 3 (1883 articles)	
	Count of domains	% (n=7060)	Count of domains	% (n=336)	Count of domains	% (n=2161)	Count of domains	% (n=4563)
A: Novel trial design	216	3.1%	38	11.3%	78	3.6%	100	2.1%
B: Pre-trial planning	1517	21.5%	23	6.9%	272	12.6%	1222	26.8%
C: Trial conduct	3336	47.3%	65	19.4%	1073	49.7%	2198	48.2%
D: Recruitment information needs	1111	15.7%	154	45.8%	479	22.2%	478	10.5%
E: Recruiter differences	607	8.6%	28	8.3%	152	7.0%	427	9.4%
F: Incentives	273	3.9%	28	8.3%	107	5.0%	138	3.0%
Total	7060	100%	336	100%	2161	100%	4563	100%
Median [IQR] domains per article	2 [1,3]		2 [1,2]		3 [2,4]		2 [1,3]	

Figure 4: Distribution of Recruitment Domains in Level 1: All articles categorised as evaluating the effectiveness of strategies or interventions (n=160)

