Recruiter Characteristics, Recruitment Strategies And The Influence On Recruitment Targets And Timelines In Randomised Controlled Trials: An Observational Retrospective Study of Ovarian Cancer Trials

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Abstract

Background

Achieving recruitment targets is a challenge to every clinical trial's success. Ovarian cancer (OC) accounted for 1.7% of all cancers diagnosed in Europe in 2012, equating to 238,719 women. As these patients have limited treatments available, it is essential that OC trials achieve their recruitment targets to prevent early termination and unanswered research questions. There is evidence to suggest that the characteristics of the recruiter has an influence on a patient's clinical trial acceptance, however there is little real world evidence to support this. The aims, and primary outcomes, of this study were to determine if recruiter characteristics reported in OC clinical trials have an influence on recruitment targets and timelines. The secondary outcome was the number of OC clinical trials with publically available recruitment strategies.

Methods

A two-step search strategy was applied to identify OC clinical trials. Searches were conducted in Cinahl, PubMed, Medline (OVID and EBSCO) and separately in the New England Journal of Medicine, American Cancer Society Journals, Lancet Oncology, Journal of Clinical Oncology and BMC Cancer and clinicaltrials.gov. Data extracted were recorded as dichotomous variables (reported=1, not reported=0).

Results

A total of 88 OC clinical trials were included. 31% (n=28) made reference to the recruiter but this was reported only in the protocol. None of the trials reviewed which closed early or extended recruitment timelines due to slow accrual reported measures taken to improve recruitment rates before stoppages or changes took place. Due to poor reporting, it is not possible to determine whether recruiter characteristics in clinical trials have any influence on recruitment targets or timelines. None of the trials included published their recruitment strategy. Two trials (2%) referred to recruitment strategies in the protocol.

Conclusions

It was not possible to determine the influence of recruiter characteristics on recruitment timelines and targets due to a lack of reporting. None of the included trials published their recruitment strategies. Reporting standards of recruiter characteristics and recruitment strategies must improve to allow identification of effective interventions and dismissal of ineffective ones. This should be done through addition to the CONSORT statement.

Background

Randomised controlled trials (RCT) are considered to be the gold standard for determining intervention efficacy (1). However, it is well documented that recruitment is a significant challenge to the success of any clinical trial (2, 3, 4, 5, 6, 7). Approximately 80% of clinical trials fail to recruit to their initial timeline

and targets, a figure which highlights the challenge for clinical trialists globally (6, 8). Failure to recruit sufficiently has resounding financial and ethical implications (5,910).

In recent years, there have been many attempts to address the recruitment challenge. Initiatives such as the Priority studies (16, 17) and systematic reviews of interventions (1, 8, 18, 19, 20, 21) have raised the profile of trials methodological research. Collaborative groups such as Trial Forge, the HRB Trials Methodology Research Network (22, 23) and the MRC-NIHR-Trials Methodology Research Partnership have been established to identify and validate recruitment strategies. Multiple methodological interventions have been trialled such as financial incentives (24), multimedia programmes (1, 25, 26, 27, 28), decision aids (29, 30, 31), follow up reminders (32, 33), optimised or modified trial information documents (34) and bespoke assessment and feedback on specific recruitment processes (35, 36, 37). These interventions have not improved recruitment significantly.

Oncology clinical trials are also blighted by poor recruitment. Globally, only 5% of oncology patients will participate in a clinical trial (11, 12). Europe contains 25% of the global cancer burden and it is expected that by 2030, 21.6 million people will be diagnosed with cancer (13). Some evidence suggests that the recruiter has an impact on a patient's decision to participate in a clinical trial (41, 45, 56, 59). However, there is no large scale evidence to support this or that it improves overall recruitment rates. We do know that "trust in the doctor" is frequently cited as a reason for trial participation (38, 39, 40, 41, 42). Although a seemingly innocuous statement, good communication, listening and interpersonal skills are factors reported to influence a patient's confidence and trust in their doctor. This is termed "alliance building" (38, 40, 43, 44, 45). Effective alliance building, such as offering support and addressing patient concerns, led to increased confidence in the doctor, trust in the treatment decision and higher clinical trial acceptance (40, 41, 42, 44, 45, 46 47, 48, 49, 50). The presence of this relationship prior to trial invitation coupled with enthusiasm shown for the trial is seen throughout the literature as a facilitator for trial acceptance (9, 45, 47, 51, 52). However, while the doctor usually takes consent, the recruitment process to that point is generally the role of the clinical research nurse (37, 40, 48, 53, 54, 55, 56, 57, 58), at least in Ireland. Therefore, eliciting information on who recruits patients could be an important factor in determining if a trial recruits to target and on time. Thus, the purpose of this study was to determine if recruiter characteristics have an influence on recruitment timelines and targets. We chose ovarian cancer (OC) clinical trials to investigate our research question. The secondary outcome was to identify the number of OC clinical trials with publically available recruitment strategies.

Methods

An observational study of OC RCTs using a retrospective design was conducted. The work had three stages.

1. Identify a body of OC trials

2. Identify publications, protocols or supplementary material associated with each trial

3. Data extraction

Stage 1 – Identify ovarian cancer trials (2010–2021)

The eligibility criteria for trials were:

- The trial was an OC clinical trial,
- The trial was Phase 3,
- The trial had finished the recruitment phase (terminated, completed, active but not recruiting),
- The trial results were published between 2010 to 2021,
- The trial could be industry or academic led
- The trial was published in English
- Full text available for inclusion.

RCTs were identified through the following journals: New England Journal of Medicine, American Cancer Society Journals, Lancet Oncology, Journal of Clinical Oncology and BMC Cancer, meaning all articles were written in English. The following databases were searched separately for eligible studies not identified through journals: Cinahl, MEDLINE (Ovid and EBSCO) and PubMed. Clinicaltrials.gov was then searched to ensure all eligible trials were identified. Search terms used included: ovarian cancer; ovarian neoplasm; clinical trial; clinical research; phase 3; randomised controlled trial; and RCT. Search terms were expanded to account for spelling differences and synonyms. An example of a search strategy can be seen in Appendix 1.

225 articles were identified through title and abstract review and saved to Zotero Reference Manager. Duplicates were removed, leaving a total of 156 articles. Trials often published several articles reporting different elements of the same trial. These articles were grouped together per trial, leaving a total of 97 trials (from 156 articles). 9 trials (and 17 published articles) were deemed ineligible on full text review. 88 trials, consisting of 139 published articles and conference abstracts were included (Fig. 1).

Stage 2: Identify other associated literature with each trial

139 articles, along with trial registries (clinicaltrials.gov, EudraCT, ISRCTN and UMIN where applicable) available protocols and supplementary information were available for data extraction. Additionally, all other published journal articles reporting elements of an included trial were reviewed to ensure full data extraction (Appendix 2). In total, 154 articles, 30 protocols, 105 trial registries and 26 trial websites were reviewed.

Stage 3: Data extraction

The data extraction sheet was piloted on five trials to ensure full data extraction would be achieved for the outcomes of interest. Data were extracted as dichotomous variable (reported = 1 not reported = 0) and continuous variables (sample size = no. of patients, enrolment period = months). Qualitative data were

extracted for reasons given for challenges or insufficient recruitment, documented recruitment aids and descriptions of recruiter characteristics (Appendix 3).

Outcomes

The primary outcomes were the effect of recruiter characteristics in OC clinical on recruitment targets and timelines.

The secondary outcome was the number of OC trials with publically available recruitment strategies.

Analysis

Analysis was simple – we reported on the presence or absence of an identified recruiter and we recorded any characteristic published. We had intended to theme these, but this was not practical given the dearth of information on recruiter characteristics. We recorded trial sample size, recruitment targets and recruitment achieved in both the protocol and the associated publication.

Results

Recruiter characteristics

Eighty-eight OC RCTs in both surgical and medical settings met the inclusion criteria.

Only 31% (n = 28) made reference to who would be recruiting and consenting the patient to the trial. This information was described in the protocol only. No mention was made of who recruited the participant to the trial in any associated publication, peer-reviewed or otherwise. Recruiter description varied between studies, often using more than one term. Terms included the principle investigator (n = 6), the investigator (n = 16), the delegate (n = 8), the surgeon (n = 1) or the “investigator who regularly treats the target population” (n = 1). One study outlined the pathway for recruitment to the trial in the protocol. This pathway outlined that the consultant gynaecologist introduced the study and the consultant radiation oncologist recruited the patient to the study (60).

While 89% (n = 79) of trials included in this review were available on at least 1 registry such as clinicaltrials.gov, only 11 of these available trials included a protocol on the registry. We had to delve further into the literature to locate other protocols published as supplementary information with a journal publication. Overall, only 45% (n = 40) of trials had published protocols available to review (clinicaltrials.gov (n = 11); supplementary information as part of the publication on NEJM or the Lancet (n = 29)). Eleven of these protocols were heavily redacted.

Trial sample size and reporting

Ninety-eight per-cent of all clinical trials reviewed stated their required sample size for the study and 100% reported the actual enrolment figure in the journal articles. However, in 6 studies, there were differences in

the reported target recruitment numbers between the protocol, the publication and the registry. Similarly, differences were noted in achieved samples sizes of 8 studies (Table 1).

Table 1
Differences in reporting targeted and achieved sample size

Trial	Target sample size-protocol	Target sample size-clinicaltrials.gov	Target sample size-publication	Achieved sample size-clinicaltrials.gov	Achieved sample size-Publication
Moore et al., 2018 (Solo1)	344	347	206 events	450	391
Walker et al., 2019 (GOG-252)	N/A	1100	1500	1560	1560
Pignata et al., 2011 (MITO-2)	N/A	530	820	820	820
Fotopoulou et al., 2014 (OVATURE)	N/A	470	340	142	142
de Boer et al., 2018 (PORTEC-3)	670	800	670	670	686
Mahner et al., 2017 (TRUST)	N/A	686	772	797	772
Vergote et al., 2010 (ASSIST-5)	N/A	224	224	244	125
van Driel et al., 2018 (HIPEC)	240	280	245	242	245
Moore and Pignata, 2019 (GOG3015)	N/A	1300	N/A	1278	1301
Monk et al., 2020 (MILO)	N/A	300	360	341	303
Oza et al., 2017 (ROSIA)	N/A	1000	NR	1021	1021
Fagotti et al., 2016 (SCORPION)	N/A	110	110	171	110
Moore et al., 2018 (Forward 1)	333	247	333	366	366

NR = not reported N/A = not available

Trial	Target sample size-protocol	Target sample size-clinicaltrials.gov	Target sample size-publication	Achieved sample size-clinicaltrials.gov	Achieved sample size-Publication
Pujade-Lauraine et al., 2017 (SOLO 2)	N/A	264	192	337	295
NR = not reported N/A = not available					

Ninety-five percent (n = 84) of trials reported the achieved recruitment timelines in an academic journal article although this was always reported from first patient randomised to last patient randomised, not time of opening to recruitment to time of closing to recruitment. Only 67% (n = 59) of all included trials reported both the planned recruitment timeline and the actual recruitment timeline in an academic journal article. 26% (n = 15/59) of these recruited for longer than planned. 8 did not report the reasons for the extended accrual period. Recruitment challenges were reported in journal articles as the reason for the extended recruitment period in 6 trials (10%). One trial reported receiving a recruitment period extension (60). Two trials subsequently closed early. Separate to recruitment challenges, one trial reported a medication supply issue which resulted in a 14 month trial suspension (61).

Fourteen per cent (n = 13) of trials were suspended, withdrawn or terminated earlier than expected. A variety of reasons were reported, often more than one, however six trials cited poor or slow accrual as the reason for closure (Fig. 2).

Fifty-one percent (n = 46) of trials recruited on target and on time. None of these trials reported the recruitment measures used to reach these targets. None of the trials which closed or extended recruitment timelines due to slow accrual reported measures taken to improve recruitment rates before stoppages or changes took place.

Recruitment strategy

60% of trials made reference to when recruitment would take place. This was described in general terms such as “prior to study registration” or “before study procedures take place”. None of the trials reported where recruitment took place. 29% reported the use of aids to assist recruitment and aids were reported as informed consent documents or procedures (patient information leaflets, informed consent forms and oral explanation). None of the trials reported the use of any other recruitment aids or specialised strategies for recruitment. Two trials had trial websites with a section for patient information available and one trial had newsletters to sites available on the trial website but these were not reported as a recruitment strategy in the protocols or published journal articles. It was unclear if these were passively available to patients or if patients were actively encouraged to engage with these materials.

None of the trials reviewed published a recruitment strategy or made reference to an available recruitment strategy for the trial. Only 2 trials made specific reference to advertisements and hospital databases as sources of recruitment in the protocol. Eight percent (n = 7) of studies referred to the opening of additional

sites if recruitment was slow, and the closure of slow recruiting sites in the published protocol, but did not define this as a recruitment strategy.

Discussion

The main purpose of this study was to identify recruiter characteristics reported in OC clinical trials and to determine if they influenced recruitment targets and timelines. From the published protocols and journal articles available, it is not possible to determine these due to poor reporting.

While 31% of the trials reviewed made reference to who would be taking consent in the protocol, the function of this information seemed primarily to ensure compliance with ICH GCP rather than to guide recruitment. Indeed, within the journal articles, the consenting process was usually described as the following: “Informed consent was obtained in line with ICH GCP and the Declaration of Helsinki”. While this is essential from an ethical perspective, it does little to address the on-going challenge trial teams face in identifying effective recruitment strategies that can be implemented as part of the site recruitment process.

A number of studies aimed to identify the barriers and facilitators to clinical trial acceptance from a patient perspective (38, 39, 40, 41, 42). Trust in the doctor and the institution is one of the most frequently cited facilitators (38, 40, 43, 44, 45), yet there are few interventions published that aim to address this and assess its effect on recruitment rates. The most successful to date is the Quintet Recruitment Intervention (QRI) (35, 37, 52, 62) but this focuses mainly on the discussion between the patient and doctor rather than the characteristics or alliance building between the two. Further studies are recommended to address this knowledge gap.

While clinician colleagues are most likely to take consent, other members of the team, such as the research nurses, are heavily involved in the recruitment process. It is difficult to assess whether the recruiter preferences reported by patients in the literature such as effective alliance building, previous relationship, trust in the institution or doctor themselves (40, 41, 42, 44, 45, 46 47, 48, 49, 50, 62) have an influence in real life multi-centre trials as the information is not available, as we have demonstrated here. The findings of this study are echoed by similar studies (5, 63, 64), highlighting that this is an issue across multiple trial settings. To determine if the person recruiting matters to the patient and to identify trends in effective recruitment relating exclusively to the personnel who undertake the task, it is essential that data related to these characteristics are captured and reported in all trial related literature.

An interesting incidental finding of this study is that there is some disparity in reporting of recruitment figures between different resources, for example, between the article and the trial registry as shown in Table 1. There could be several reasons for this: 1. the registry is incorrectly updated, possibly due to human error; 2. the most recent protocol version may not be published and therefore the information available could be out-dated; 3.it could be that the clinicaltrials.gov registry lists the “actual enrolment figure” which could be interpreted in different ways. It could be interpreted as the number of patients who signed consent or the number who proceeded to the treatment phase. This disparity in reporting is

misleading for researchers, patients and the public alike. OC clinical trials have vastly varying screen failure rates. This is due to disease burden, increasingly biomarker led studies and narrow inclusion criteria (11, 12). Not every patient who signs consent is eligible to proceed to the treatment phase. Therefore, it is essential that the term “actual enrolment figure” is clarified on clinical trials.gov and clearly outlines whether it refers to the number of patients who signed consent or the number who proceeded to the treatment phase. Additionally, it should be common practice that the protocol and all its amendments are published.

Similar to previous studies (10, 20, 63, 64), none of the trials reviewed reported sufficient information to evaluate recruitment strategies in the protocols or published journal articles. This contradicts the recommendations of item 15 of the SPIRIT statement (65). However, there is evidence that recruitment strategies were used by trial sponsors. For example, some trials were found to have trial websites with specific sections for patient information but did not report these in the published literature. Thus, no information exists as to how effective this resource is as a decision aid for patients and a recruitment tool for the trial. Poor reporting of strategies and timelines has led to a missed opportunity to identify effective interventions. Publication of detailed recruitment strategies should be a requirement of the CONSORT statement as an expansion of sections 4b and 14a, (66) to guide further methodological research.

Strengths And Limitations

This study highlights poor recruitment reporting practices in OC trials and has emphasised that despite a heightened focus by methodologists on recruitment interventions, international OC trials lag behind in reporting their recruitment strategies. The study includes all phase 3 OC trials for more than a decade. A limitation of this study is that search strategies and data extraction were not completed in duplicate. However, this was not a systematic review, and the methods here do not change the findings of the study.

Conclusion

It was not possible to determine the influence of recruiter characteristics on OC trials recruitment or recruitment timelines due to insufficient reporting. No OC trials published a recruitment strategy. It is recommended that reporting standards surrounding trial recruitment should improve, through addition to the CONSORT statement. Recruitment strategies should be published, and more detail, including characteristics of the recruiters, should be published to aid identification of effective interventions, dismissal of ineffective ones and to determine whether the characteristics of those involved in the recruitment process at a site level influences the recruitment success of a trial. Clarity on what a recruitment timeline is, i.e., trial open to close versus first patient randomised to last patient, is also needed. By improving reporting practices, it may be possible to identify key characteristics that will inform staff training and development and, through successful recruitment, improve patient care and outcomes in ovarian cancer.

Declarations

Ethics approval and consent to participate

This was a retrospective study of existing publically available research therefore ethical approval was not required.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

EOSG undertook this research project in part-fulfilment of her MSc Clinical Trials. FS conceptualised the research project, supervised the research and commented on multiple drafts.

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References

1. Delaney H, Devane D, Hunter A, Hennessy M, Parker A, Murphy L, et al. Limited evidence exists on the effectiveness of education and training interventions on trial recruitment; a systematic review.

Journal of Clinical Epidemiology. 2019 Sep 1;113:75–82.

2. Mc Daid, C., Hodges, Z., Fayter, D., Stirk, L., Eastwood, A. (2006) Increasing participation of cancer patients in randomised controlled trials: a systematic review. Trials 7, 16. https://doi.org/10.1186/1745-6215-7-16
3. Albrecht TL, Eggly SS, Gleason MEJ, Harper FWK, Foster TS, Peterson AM, et al. Influence of clinical communication on patients' decision making on participation in clinical trials. J Clin Oncol. 2008 Jun 1;26(16):2666–73.
4. Sully, B.G.O., Julious, S.A., Nicholl, J. (2013) A reinvestigation of recruitment to randomised, controlled, multicenter trials: a review of trials funded by two UK funding agencies. Trials 14, 166. https://doi.org/10.1186/1745-6215-14-166
5. Briel M, Speich B, von Elm E, Gloy V. Comparison of randomized controlled trials discontinued or revised for poor recruitment and completed trials with the same research question: a matched qualitative study. Trials. 2019 Dec 30;20(1):1–12.
6. Desai M. Recruitment and retention of participants in clinical studies: Critical issues and challenges. Perspect Clin Res. 2020;11(2):51–3.
7. Pinto BM, Dunsiger SI. The many faces of recruitment in a randomized controlled trial. Contemporary Clinical Trials. 2021 Mar 1;102:106285.
8. Brøgger-Mikkelsen M, Ali Z, Zibert JR, Andersen AD, Thomsen SF. Online Patient Recruitment in Clinical Trials: Systematic Review and Meta-Analysis. Journal of Medical Internet Research [Internet]. 2020 [cited 2021 Apr 16];22(11). Available from: https://journals.scholarsportal.info/details/14394456/v22i0011/nfp_oprictsram.xml
9. Fletcher B, Gheorghe A, Moore D, Wilson S, Damery S. Improving the recruitment activity of clinicians in randomised controlled trials: a systematic review. BMJ Open. 2012 Jan 1;2(1):e000496.
10. Unger JM, Cook E, Tai E, Bleyer A. Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ Book. 2016;35:185–98.
11. C Kelly, M Smith, S Flynn, A Reyes, M Higgins, J McCaffrey, C Kelly. Accrual to Cancer Clinical Trials – Irish Medical Journal [Internet]. 2016 [cited 2021 Mar 5]. Available from: http://imj.ie/accrual-to-cancer-clinical-trials/
12. Nathe JM, Krakow EF. The Challenges of Informed Consent in High-Stakes, Randomized Oncology Trials: A Systematic Review. MDM Policy Pract [Internet]. 2019 Mar 28 [cited 2021 Feb 8];4(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6440043/
13. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. European Journal of Cancer. 2018 Nov;103:356–87.
14. Allemani C, Matsuda T, Di Carlo V, Harewood R, Matz M, Nikšić M, et al. Global surveillance of trends in cancer survival 2000–14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. The Lancet. 2018 Mar 17;391(10125):1023–75.

15. National Cancer Registry Ireland (2020) Cancer in Ireland 1994-2018 with estimates for 2018-2020: Annual report of the National Cancer Registry. NCRI, Cork, Ireland.
16. Healy P, Galvin S, Williamson PR, Treweek S, Whiting C, Maeso B, et al. Identifying trial recruitment uncertainties using a James Lind Alliance Priority Setting Partnership – the PRioRiTy (Prioritising Recruitment in Randomised Trials) study. Trials. 2018 Mar 1;19(1):147.
17. Brunsdon D, Biesty L, Brocklehurst P, Brueton V, Devane D, Elliott J, et al. What are the most important unanswered research questions in trial retention? A James Lind Alliance Priority Setting Partnership: the PRioRiTy II (Prioritising Retention in Randomised Trials) study. Trials. 2019 Oct 15;20(1):593.
18. Crocker JC, Ricci-Cabello I, Parker A, Hirst JA, Chant A, et al. Impact of patient and public involvement on enrolment and retention in clinical trials: systematic review and meta-analysis. BMJ : British Medical Journal (Online) [Internet]. 2018 Nov 28 [cited 2021 Apr 16];363. Available from: http://search.proquest.com/docview/2139014172/abstract/96F6929127094265PQ/1
19. Rowlands C, Rooshenas L, Fairhurst K, Rees J, Gamble C, Blazeby JM. Detailed systematic analysis of recruitment strategies in randomised controlled trials in patients with an unscheduled admission to hospital. BMJ Open [Internet]. 2018 [cited 2021 Apr 16];8(2). Available from: https://journals.scholarsportal.info/details/20446055/v08i0002/nfp_dsaorswauath.xml
20. Treweek S, Pitkethly M, Cook J, Fraser C, Mitchell E, Sullivan F, et al. Strategies to improve recruitment to randomised trials. Cochrane Database Syst Rev [Internet]. 2018 Feb 22 [cited 2021 Feb 12];2018(2). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7078793/
21. Bracken K, Askie L, Keech AC, Hague W, Wittert G. Recruitment strategies in randomised controlled trials of men aged 50 years and older: a systematic review. BMJ Open [Internet]. 2019 [cited 2021 Apr 16];9(4). Available from: https://journals.scholarsportal.info/details/20446055/v09i0004/nfp_rsirctyaoasr.xml
22. Hanrahan V, Gillies K, Biesty L. Recruiters' perspectives of recruiting women during pregnancy and childbirth to clinical trials: A qualitative evidence synthesis. PLOS ONE. 2020 Jun 19;15(6):e0234783.
23. Houghton C, Dowling M, Meskell P, Hunter A, Gardner H, Conway A, et al. Factors that impact on recruitment to randomised trials in health care: a qualitative evidence synthesis. Cochrane Database of Systematic Reviews [Internet]. 2020 [cited 2021 Apr 25];(10). Available from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.MR000045.pub2/full
24. Krutsinger DC, McMahon J, Stephens-Shields AJ, Bayes B, Brooks S, Hitsman BL, et al. Randomized evaluation of trial acceptability by INcentive (RETAIN): Study protocol for two embedded randomized controlled trials. Contemporary Clinical Trials. 2019 Jan 1;76:1–8.
25. Hutchison C, Cowan C, McMahon T, Paul J. A randomised controlled study of an audiovisual patient information intervention on informed consent and recruitment to cancer clinical trials. British Journal of Cancer. 2007 Sep;97(6):705–11.
26. Hoffner B, Bauer-Wu S, Hitchcock-Bryan S, Powell M, Wolanski A, Joffe S. "Entering a clinical trial: Is it right for you?" Cancer. 2012;118(7):1877–83.

27. Ditai J, Kanyago J, Nambozo MR, Odeke NM, Abeso J, Dusabe-Richards J, et al. Optimising informed consent for participants in a randomised controlled trial in rural Uganda: a comparative prospective cohort mixed-methods study. Trials. 2018 Dec 22;19(1):699.
28. Lipstein EA, Breslin M, Dodds CM, Kappelman MD, Ollberding NJ, Margolis P, et al. Integrating shared decision making into trial consent: A nested, cluster-randomized trial. Patient Education and Counseling [Internet]. 2020 Dec 25 [cited 2021 Feb 20]; Available from: https://www.sciencedirect.com/science/article/pii/S0738399120306820
29. Fisher L, Hessler D, Naranjo D, Polonsky W. AASAP: A program to increase recruitment and retention in clinical trials. Patient Education and Counseling. 2012 Mar 1;86(3):372–7.
30. Juraskova I, Butow P, Bonner C, Bell ML, Smith AB, Seccombe M, et al. Improving decision making about clinical trial participation – a randomised controlled trial of a decision aid for women considering participation in the IBIS-II breast cancer prevention trial. British Journal of Cancer. 2014 Jul;111(1):1–7.
31. Politi MC, Kuzemchak MD, Kaphingst KA, Perkins H, Liu J, Byrne MM. Decision Aids Can Support Cancer Clinical Trials Decisions: Results of a Randomized Trial. Oncologist. 2016 Dec;21(12):1461–70.
32. Aaronson NK, Visser-Pol E, Leenhouts GH, Muller MJ, van der Schot AC, van Dam FS, et al. Telephone-based nursing intervention improves the effectiveness of the informed consent process in cancer clinical trials. JCO. 1996 Mar 1;14(3):984–96.
33. Gillies K, Chalmers I, Glasziou P, Elbourne D, Elliott J, Treweek S. Reducing research waste by promoting informed responses to invitations to participate in clinical trials. Trials. 2019 Oct 28;20(1):613.
34. Parker A, Knapp P, Treweek S, Madhurasinghe V, Littleford R, Gallant S, et al. The effect of optimised patient information materials on recruitment in a lung cancer screening trial: an embedded randomised recruitment trial. Trials. 2018 Sep 18;19(1):503.
35. Donovan JL, Rooshenas L, Jepson M, Elliott D, Wade J, Avery K, et al. Optimising recruitment and informed consent in randomised controlled trials: the development and implementation of the Quintet Recruitment Intervention (QRI). Trials. 2016 Jun 8;17(1):283.
36. Wuensch A, Goelz T, Ihorst G, Terris DD, Bertz H, Bengel J, et al. Effect of individualized communication skills training on physicians' discussion of clinical trials in oncology: results from a randomized controlled trial. BMC Cancer. 2017 Apr 13;17:1–9.
37. Rooshenas L, Scott LJ, Blazeby JM, Rogers CA, Tilling KM, Husbands S, et al. The QuinteT Recruitment Intervention supported five randomized trials to recruit to target: a mixed-methods evaluation. Journal of Clinical Epidemiology. 2019 Feb 1;106:108–20.
38. Jenkins V, Fallowfield L. Reasons for accepting or declining to participate in randomized clinical trials for cancer therapy. British Journal of Cancer. 2000 Jun;82(11):1783–8.
39. Kass NE, Sugarman J, Medley AM, Fogarty LA, Taylor HA, Daugherty CK, et al. An Intervention to Improve Cancer Patients' Understanding of Early-Phase Clinical Trials. IRB. 2009;31(3):1–10.

40. Siminoff LA. Why Learning to Communicate With Our Patients Is So Important: Using Communication to Enhance Accrual to Cancer Clinical Trials. Journal of Clinical Oncology [Internet]. 2016 Sep 21 [cited 2021 Apr 10]; Available from: https://ascopubs.org/doi/pdf/10.1200/JCO.2008.16.2610
41. Berrios C, James CA, Raraigh K, Bollinger J, Murray B, Tichnell C, et al. Enrolling Genomics Research Participants through a Clinical Setting: the Impact of Existing Clinical Relationships on Informed Consent and Expectations for Return of Research Results. Journal of Genetic Counseling. 2018 Feb;27(1):263–73.
42. Kao C-Y, Aranda S, Krishnasamy M, Hamilton B. Identifying essential information to support patient decision-making regarding participation in cancer clinical trials: A Delphi study. European Journal of Cancer Care. 2018;27(6):e12954.
43. Albrecht TL, Blanchard C, Ruckdeschel JC, Coovert M, Strongbow R. Strategic Physician Communication and Oncology Clinical Trials. JCO. 1999 Oct 1;17(10):3324–32.
44. Albrecht TL, Eggly SS, Gleason MEJ, Harper FWK, Foster TS, Peterson AM, et al. Influence of clinical communication on patients' decision making on participation in clinical trials. J Clin Oncol. 2008 Jun 1;26(16):2666–73.
45. Curbow B, Fogarty LA, McDonnell KA, Chill J, Scott LB. The Role of Physician Characteristics in Clinical Trial Acceptance: Testing Pathways of Influence. Journal of Health Communication. 2006 Mar 1;11(2):199–218.
46. Adams SA, Heiney SP, Brandt HM, Wirth MD, Khan S, Johnson H, et al. A Comparison of a Centralized Versus De-centralized Recruitment Schema in Two Community-Based Participatory Research Studies for Cancer Prevention. J Community Health. 2015 Apr 1;40(2):251–9.
47. Albrecht TA, Taylor AG. No stone left unturned: Challenges encountered during recruitment of women with advanced ovarian cancer for a phase I study. Applied Nursing Research. 2013 Nov 1;26(4):245–50.
48. Morgan SE, Occa A, Mouton A, Potter J. The Role of Nonverbal Communication Behaviors in Clinical Trial and Research Study Recruitment. Health Communication. 2017 Apr 3;32(4):461–9.
49. Sheridan R, Martin-Kerry J, Hudson J, Parker A, Bower P, Knapp P. Why do patients take part in research? An overview of systematic reviews of psychosocial barriers and facilitators. Trials. 2020 Mar 12;21(1):259.
50. Schwaegermann M-K, Schranz M, Moehler M, Labenz C, Moringlane A, Schmidt M, et al. Any progress in informed consenting for cancer treatment? Results from a cross sectional analysis at a comprehensive cancer center. J Cancer Res Clin Oncol [Internet]. 2021 Jan 9 [cited 2021 Feb 8]; Available from: https://doi.org/10.1007/s00432-020-03495-1
51. Cox K. Informed consent and decision-making: patients' experiences of the process of recruitment to phases I and II anti-cancer drug trials. Patient Education and Counseling. 2002 Jan 1;46(1):31–8.
52. Conefrey C, Donovan J l., Stein R c., Paramasivan S, Marshall A, Bartlett J, et al. Strategies to Improve Recruitment to a De-escalation Trial: A Mixed-Methods Study of the OPTIMA Prelim Trial in Early

Breast Cancer. Clinical Oncology. 2020 Jun;32(6):382–9.

53. Donovan JL, Peters TJ, Noble S, Powell P, Gillatt D, Oliver SE, et al. Who can best recruit to randomized trials?: Randomized trial comparing surgeons and nurses recruiting patients to a trial of treatments for localized prostate cancer (the ProtecT study). Journal of Clinical Epidemiology. 2003 Jul 1;56(7):605–9.
54. Monson K, Parlour L, Simcock R, Fallowfield L, Jenkins V. Group recruitment sessions enhance patient understanding in a small multi-centre phase III clinical trial. Contemporary Clinical Trials. 2012 Mar 1;33(2):286–90.
55. Cresswell P, Gilmour J. The Informed Consent Process in Randomised Controlled Trials: A Nurse-Led Process. Nursing Praxis in New Zealand. 2014 Mar;30(1):17–28.
56. Heller C, Balls-Berry JE, Nery JD, Erwin PJ, Littleton D, Kim M, et al. Strategies Addressing Barriers to Clinical Trial Enrollment of Underrepresented Populations: a Systematic Review. Contemp Clin Trials. 2014 Nov;39(2):169–82.
57. Newington L, Metcalfe A. Factors influencing recruitment to research: qualitative study of the experiences and perceptions of research teams. BMC Med Res Methodol. 2014 Jan 23;14:10.
58. Flocke SA, Antognoli E, Daly BJ, Jackson B, Fulton SE, Liu TM, et al. The Role of Oncology Nurses in Discussing Clinical Trials. Oncology Nursing Forum. 2017 Sep 1;44(5):547–52.
59. Besle S, Schultz E, Hollebecque A, Varga A, Baldini C, Martin P, et al. Organisational factors influencing early clinical trials enrollment: Gustave Roussy experience. European Journal of Cancer. 2018 Jul 1;98:17–22.
60. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018 Mar;19(3):295–309.
61. Marth C, Vergote I, Scambia G, Oberaigner W, Clamp A, Berger R, et al. ENGOT-ov-6/TRINOVA-2: Randomised, double-blind, phase 3 study of pegylated liposomal doxorubicin plus trebananib or placebo in women with recurrent partially platinum-sensitive or resistant ovarian cancer. European Journal of Cancer. 2017;70(Complete):111–21.
62. Sherratt FC, Brown SL, Haylock BJ, Francis P, Hickey H, Gamble C, et al. Challenges Conveying Clinical Equipoise and Exploring Patient Treatment Preferences in an Oncology Trial Comparing Active Monitoring with Radiotherapy (ROAM/EORTC 1308). Oncologist. 2020 Apr;25(4):e691–700.
63. Mitchell AP, Hirsch BR, Abernethy AP. Lack of timely accrual information in oncology clinical trials: a cross-sectional analysis. Trials. 2014 Mar 25;15(1):92.
64. Trung LQ, Morra ME, Truong ND, Turk T, Elshafie A, Foly A, et al. A systematic review finds underreporting of ethics approval, informed consent, and incentives in clinical trials. Journal of Clinical Epidemiology. 2017 Nov 1;91:80–6.
65. Chan, A.-W., Tetzlaff, J.M., Gøtzsche, P.C., Altman, D.G., Mann, H., Berlin, J.A., Dickersin, K., Hróbjartsson, A., Schulz, K.F., Parulekar, W.R., Krleža-Jerić, K., Laupacis, A., Moher, D., (2013). SPIRIT

2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 346, e7586. https://doi.org/10.1136/bmj.e7586

66. Schulz KF, Altman DG, Moher D. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010 Mar 24;340:c332.

Figures

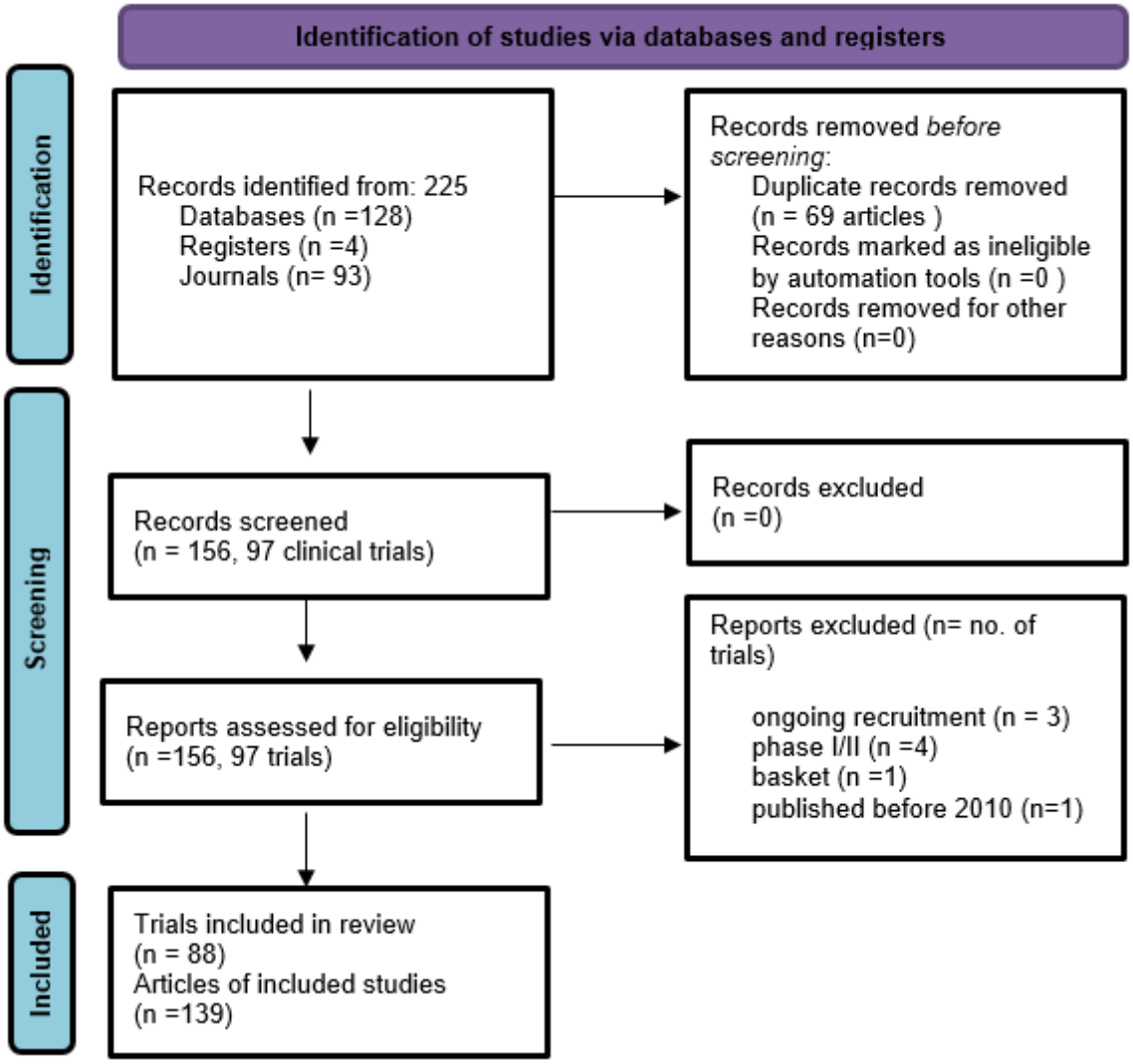

Figure 1

PRISMA flow chart

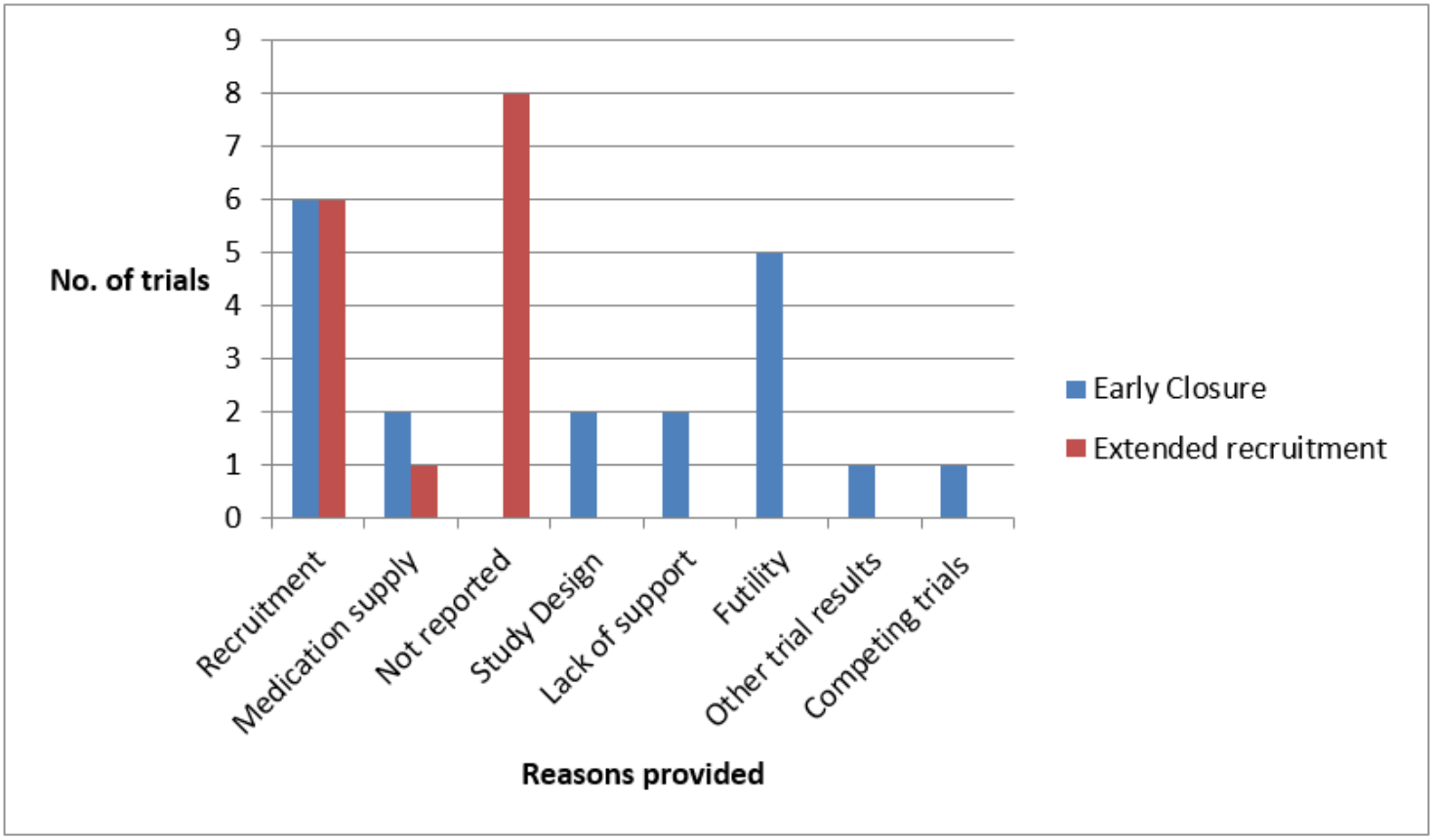

Figure 2

Reasons for trial closure and extended recruitment periods.

Supplementary Files

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- Appendices.docx
- STROBEchecklistFinal.docx